100.0% PROCESSED 37182 ITERATIONS 594 ANSWERS
SEARCH TIME: 00.00.01

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     (FILE 'HOME' ENTERED AT 07:01:07 ON 04 MAR 2003)
               SET COST OFF

     FILE 'REGISTRY' ENTERED AT 07:01:40 ON 04 MAR 2003
L1             STR
L2          19 S L1
L3         594 S L1 FUL
               SAV L3 KWON071/A

     FILE 'HCAPLUS' ENTERED AT 07:07:47 ON 04 MAR 2003
L4          40 S L3
               E BUSER S/AU
L5          10 S E3,E6,E7
               E FORD A/AU
L6          33 S E3,E16,E17
L7          37 S E63,E65
               E FORD TONY/AU
               E HOFFMANN T/AU
L8         135 S E3-E9
               E HOFFMANN TOR/AU
L9          57 S E4
               E LENZ B/AU
L10         29 S E3-E9
               E SLEIGHT A/AU
L11         52 S E4,E6-E8
               E VANKAN P/AU
L12         23 S E3-E5
               E ROCHE/PA,CS
L13      21472 S E3,E4
L14         61 S E27-E46
               E ROHAN/PA,CS
L15          2 S E3,E4
L16         10 S L4 AND L5-L15
               E PROSTATE/CT
               E E5+ALL
L17       2309 S E2
L18       1988 S E12
L19      22609 S E20-E19+NT
L20          1 S L4 AND L17-L19
L21          1 S L4 AND (BPH OR BENIGN (L) PROSTAT? (L) (HYPERPLAS? OR HYPERTR
L22          1 S L20,L21
L23          1 S L22 AND L16
L24        969 S (NK OR NEUROKININ OR NEURO KININ)()1 (L) RECEPTOR (L) (ANTAGO
L25          5 S L24 AND L17-L19
L26          2 S L24 AND (BPH OR BENIGN (L) PROSTAT? (L) (HYPERPLAS? OR HYPERT
L27          6 S L25,L26
L28          1 S L23 AND L27
L29          5 S L27 NOT L28
               SEL DN AN 1 4 5
L30          3 S E1-E7 AND L29
L31          4 S L28,L30 AND (NK OR NK1 OR NEUROKININ OR TACHYKIN? OR RECEPTOR
L32          4 S L28,L30,L31
L33         39 S L4 AND (PD<=20010423 OR PRD<=20010423 OR AD<=20010423)
L34         47 S GR205171 OR GR()(205171 OR 205 171)
L35          5 S HSP117 OR HSP 117
L36         36 S L703606 OR L()(703606 OR 703 606)
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L37          23 S L668169 OR L()(668169 OR 668 169)
L38           4 S LY303241 OR LY()(303241 OR 303 241)
L39          12 S LY306740 OR LY()(306740 OR 306 740)
L40          21 S MK869 OR MK 869
L41           6 S R544 OR R 544
L42           5 S SPANTIDE III
L43          11 S WIN62577 OR WIN()(62577 OR 62 577)
L44           5 S GR103537 OR GR()(103537 OR 103 537)
L45          13 S L758298 OR L()(758298 OR 758 298)
L46           9 S NKP608 OR NKP 608
L47          17 S CGP49823 OR CGP()(49823 OR 49 823)
L48         494 S CP96345 OR CP()(96345 OR 96 345)
L49         246 S CP99994 OR CP()(99994 OR 99 994)
L50          24 S CP122721 OR CP()(122721 OR 122 721)
L51         129 S FK888 OR FK 888
L52         119 S GR82334 OR GR()(82334 OR 82 334)
L53          41 S GR94800 OR GR()(94800 OR 94 800)
L54          20 S L733060 OR L()(733060 OR 733 060)
L55          16 S L742694 OR L()(742694 OR 742 694)
L56          10 S L754030 OR L()(754030 OR 754 030)
L57          30 S LY303870 OR LY()(303870 OR 303 870)
L58           9 S MEN11149 OR MEN()(11149 OR 11 149)
L59          10 S PD154075 OR PD()(154075 OR 154 075)
L60         250 S RP67580 OR RP()(67580 OR 67 580)
L61          18 S RPR100893 OR RPR()(100893 OR 100 893)
L62           1 S SPENDIDE
L63          32 S SENDIDE
L64          55 S SPANTIDE II
L65         217 S SR140333 OR SR()(140333 OR 140 333)
L66           0 S WIN41708 OR WIN()(41708 OR 41 708)
L67          11 S WIN62577 OR WIN()(62577 OR 62 577)
L68         410 S SR48968 OR SR()(48968 OR 48 968)
L69          69 S L659877 OR L()(659877 OR 659 877)
L70          74 S MEN10627 OR MEN()(10627 OR 10 627)
L71          14 S SR144190 OR SR()(144190 OR 144 190)
L72          41 S GR94800 OR GR()(94800 OR 94 800)
L73         149 S SR142801 OR SR()(142801 OR 142 801)
L74         159 S R820 OR R 820
L75          14 S R486 OR R 486
L76          13 S SB222200 OR SB()(222200 OR 222 200)
L77          13 S L758298 OR L()(758298 OR 758 298)
L78           0 S NK608 OR NK 608
L79           3 S MK608 OR MK 608
L80           2 S CGP47899 OR CGP()(47899 OR 47 899)
L81          16 S MEN11467 OR MEN()(11467 OR 11 467)
L82          18 S GR203040 OR GR()(203040 OR 203 040)
L83          13 S L732138 OR L()(732138 OR 732 138)
L84           1 S L4 AND L34-L83
L85           2 S WIN41908 OR WIN()(41908 OR 41 908)
L86         349 S SPANTIDE
L87           1 S L4 AND L85,L86
L88           1 S L84,L87
                SEL RN

     FILE 'REGISTRY' ENTERED AT 07:50:53 ON 04 MAR 2003
L89         186 S E8-E193
L90         129 S L89 AND L3
L91           1 S 351383-26-1
L92          56 S L89 NOT L90,L91
L93           7 S 123-90-0 OR 3282-30-2 OR 4548-45-2 OR 16419-60-6 OR 139911-29
L94           6 S 471938-15-5 OR 474026-15-8 OR 474026-16-9 OR 474026-17-0 OR 4
L95          43 S L92 NOT L93,L94
L96           6 S 144177-32-2 OR 351383-26-1 OR 170729-80-3 OR 145194-26-9 OR 1
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     FILE 'REGISTRY' ENTERED AT 07:57:44 ON 04 MAR 2003
L97           46 S L95,L96

     FILE 'HCAPLUS' ENTERED AT 07:58:26 ON 04 MAR 2003
L98          964 S L97
L99            3 S L4 AND L98
L100           3 S L88,L99
L101           3 S L100 AND L4-L16
L102           6 S L32,L101
                 E TACKYKININ RECEPTOR/CT
                 E TACHYKININ RECEPTOR/CT
L103        1581 S E5,E6
L104         223 S E14
                 E E4+ALL
L105        3707 S E10,E11,E9+NT
                 E E27+ALL
L106        2037 S E8,E7+NT
                 E E6+ALL
L107        3401 S E7,E8,E6+NT
                 E E20
L108        2087 S E3-E21
L109         638 S E22-E25
L110          13 S L4 AND L103-L109
L111           3 S L102 AND L110
L112           6 S L102,L111
L113           6 S L112 AND L4-L88
L114           3 S L113 AND L17-L19
L115           2 S L113 AND (BHP OR BENIGN(L)PROSTAT?(L)HYPER?)
L116           4 S L114,L115
L117          12 S L110,L113 NOT L116
L118          12 S L117 AND L4-L88,L98-L109

     FILE 'REGISTRY' ENTERED AT 08:04:28 ON 04 MAR 2003

=> fil hcaplus
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FILE COVERS 1907 - 4 Mar 2003  VOL 138 ISS 10
FILE LAST UPDATED: 3 Mar 2003  (20030303/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


=> d l116 all tot

L116 ANSWER 1 OF 4  HCAPLUS  COPYRIGHT 2003 ACS
AN   2003:151546  HCAPLUS
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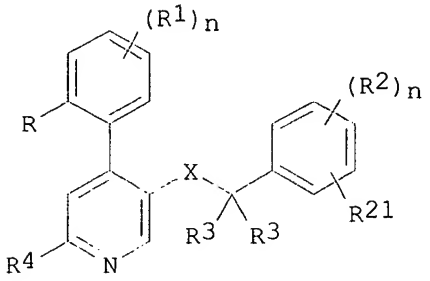
TI New approaches in the treatment of overactive bladder: Targeting adrenergic **receptors** and **neurokinin receptors**
AU Ishizuka, O.
CS Department of Urology, Shinshu University School of Medicine, Matsumoto, 390-8621, Japan
SO Current Medicinal Chemistry: Central Nervous System Agents (2003), 3(1), 43-47
CODEN: CMCCCO; ISSN: 1568-0150
PB Bentham Science Publishers Ltd.
DT Journal
LA English
CC 1 (Pharmacology)
AB Bladder outlet obstruction, such as **benign prostatic hypertrophy**, and neurogenic bladder with cerebro-vascular disease and Parkinson's disease, not only cause difficulty in urination, but also overactive bladder. This overactive condition is currently a major health concern, in terms of quality of life. Bladder outlet obstruction leads to bladder **hypertrophy**, and changes in the nervous control of micturition. **Hypertrophied** detrusor muscles release nerve growth factor, which also leads to changes in nervous control of micturition, esp. sympathetic nerve and c-fiber mediated control. Adrenergic **receptors** comprise certain subtypes, .alpha.1A, .alpha.1B, .alpha.1D, .alpha.2A, .alpha.2B, .alpha.2D, .beta.1, .beta.2, .beta.3. Recently, .alpha.1D and .beta.3 **receptors** are of particular interest with regard to their functional role in overactive bladder. **Tachykinins** are the main neuropeptides of c-fiber mediated nervous control. Normally, this c-fiber is silent; however, in pathol. conditions, such as bladder outlet obstruction and neurogenic bladder, it becomes activated and causes overactive bladder. Recently, **antagonists** of **tachykinin receptors**, **neurokinin** (**NK**) 1, 2, 3, have become of interest in regard to their role in the treatment of overactive bladder. This review describes some of the changes in adrenergic and **NK receptors** in the central nervous system and the spinal micturition center in the overactive bladder, and a new approach to treatment that targets these **receptors**.

L116 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2003 ACS
AN 2002:832668 HCAPLUS
DN 137:337901
TI Preparation and use of amides as **NK-1 receptor antagonists** against **benign prostatic hyperplasia**
IN **Buser, Susanne; Ford, Anthony P. D. W.; Hoffmann, Torsten; Lenz, Barbara; Sleight, Andrew John; Vankan, Pierre**
PA F. Hoffmann-La **Roche** A.-G., Switz.
SO PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61P013-08
ICS A61K031-44; A61K031-455
CC 28-14 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 27
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI WO 2002085458 | A2 | 20021031 | WO 2002-EP1085 | 20020202 <-- |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL,

PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,
UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 2003004157 A1 20030102 US 2002-71570 20020208 <--
PRAI EP 2001-109853 A 20010423 <--
OS MARPAT 137:337901
GI



I

AB Use of an **NK-1 receptor antagonist** for the treatment or prevention of **benign prostatic hyperplasia** (**BPH**) is claimed. The preferred **NK -1 receptor antagonists** are compds. of the general formula [I; R = H, alkyl, alkoxy, halo, CF3; R1 = H, halo; RR1 = CH:CHCH:CH; R2, R21 = H , halo , CF3, alkyl, alkoxy, cyano; R2R21 = CH:CHCH:CH, optionally substituted by 1-2 alkyl, halo, alkoxy; R3 = H, alkyl; R3R3C = cycloalkyl; R4 = H, N(R5)2, NR5(CH2)nOH, cyclic tertiary amine, etc.; X = CONR5, (CH2)pO, NR5(CH2)p, etc.; R5 = H, cycloalkyl, Ph, PhCH2, alkyl; n = 0-4; p = 1-3]. Preferred compds. are 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)isobutyramide, 3-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]isobutyramide, 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1.lambda.6-thiomorpholin-4-yl)-4-o-tolyl-pyridin-3-yl]-N-methylisobutyramide, and 2-(3,5-bis-trifluoromethylphenyl)-N-[6-(1,1-dioxo-1.lambda.6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methylisobutyramide. Thus, 2-[3,5-bis(trifluoromethyl)phenyl]-N-methyl-N-(6-thiomorpholin-4-yl-4-o-tolylpyridin-3-yl)isobutyramide (prepn. given) oxone were stirred 2 days at room temp. to give 2-(3,5-bis-trifluoromethylphenyl)-N-[6-(1,1-dioxo-1.lambda.6-thiomorpholin-4-yl)-4-o-tolylpyridin-3-yl]-N-methylisobutyramide. 2-(3,5-Bistrifluoromethylphenyl)-N-methyl-N-methyl-N-(6-morpholin-4-yl-4-o-tolylpyridin-3-yl)isobutyramide at 60 mg/kg/day orally in dogs reduced **prostate** wt. by 58% after 39 wk.

ST amide prepn **benign prostatic hypertrophy** treatment; **nk1 receptor** antagonist amide prepn; **benign prostatic hypertrophy** treatment pyridylamide

IT **Tachykinin receptors**
(**NK1 antagonists**; prepn. and use of amides as **NK-1 receptor antagonists** against **benign prostatic hyperplasia**)

IT **Prostate gland**
(**benign hyperplasia**, treatment; prepn. and use of amides as **NK-1 receptor antagonists** against **benign prostatic hyperplasia**)

IT Human
(prepn. and use of amides as **NK-1 receptor**

antagonists against benign prostatic hyperplasia)

IT 474026-03-4P 474026-04-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and use of amides as NK-1 receptor antagonists against benign prostatic hyperplasia)

IT 66619-84-9, WIN-41908 91224-37-2, Spantide 125989-12-0, L-659877 126088-92-4, R 544 129176-97-2, Spantide II 129623-01-4, GR 82334 132041-95-3, R486 132746-60-2, CP-96345 135911-02-3, RP-67580 136982-36-0, CP-99994 137012-28-3, L 668169 138449-07-7, FK 888 141636-65-9, GR 94800 142001-63-6, SR-48968 144177-32-2, WIN-62577 144425-84-3, L 703606 145742-28-5, CP-122721 148451-96-1, L 732138 148700-85-0, L 733060 150705-88-7, CGP49823 153438-49-4, RPR 100893 154427-06-2, Spantide III 155418-05-6, SR 140333 157351-81-0, MEN 10627 158991-23-2, PD 154075 159706-39-5, L 742694 168266-90-8, GR205171 168398-02-5, GR203040 170566-51-5, LY 303241 170566-84-4, LY 303870 170567-08-5, LY 306740 170729-80-3, MK-869 172673-20-0, L 758298 173050-51-6, SR-142801 173481-41-9, CGP 47899 174635-69-9, SB222200 177707-12-9, NKP608 183673-27-0, HSP -117 201152-86-5, SR 144190 206052-25-7, MEN 11149 214487-46-4, MEN 11467 240436-53-7, MK 608 290296-41-2 290296-42-3 290296-43-4 290296-44-5 290296-45-6 290296-46-7 290296-47-8 290296-49-0 290296-50-3 290296-51-4 290296-59-2 290296-66-1 290296-67-2 290296-68-3 290296-71-8 290296-72-9 290296-73-0 290296-74-1 290296-75-2 290296-86-5 290296-87-6 290296-88-7 290296-89-8 290296-90-1 290296-91-2 290296-92-3 290296-93-4 290296-94-5 290296-95-6 290296-96-7 290296-98-9 290296-99-0 290297-00-6 290297-01-7 290297-06-2 290297-18-6 290297-26-6 290297-30-2 290297-57-3 290297-58-4 290297-59-5 290297-61-9 290297-62-0 290297-65-3 290298-21-4 351383-26-1, GR 103537 391674-73-0 391674-74-1 391674-75-2 391674-76-3 391674-77-4 391674-79-6 391674-80-9 391674-81-0 391674-82-1 391674-83-2 391674-84-3 391674-85-4 391674-86-5 391674-87-6 391674-89-8 391674-90-1 391674-91-2 391674-92-3 391674-93-4 391674-94-5 391674-95-6 391674-97-8 391674-98-9 391674-99-0 391675-00-6 391675-01-7 391675-02-8

E 45
E 185-187
E 163
E 91

**393508-70-8 393508-71-9 393508-72-0**
**393508-73-1 393508-74-2 393508-75-3**
**393508-76-4 393508-77-5 393508-78-6**
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**401891-44-9 401891-45-0 401891-55-2**
**401891-63-2 401891-67-6 401891-70-1**
**401891-87-0 401891-90-5 401891-91-6**
**401891-94-9 401892-00-0 401892-10-2**
**401892-12-4 401892-24-8 401892-25-9**
**401892-29-3 401892-38-4 401892-63-5**
**474026-05-6 474026-06-7 474026-07-8**
**474026-08-9 474026-09-0 474026-10-3**
**474026-11-4 474026-12-5 474026-13-6**
**474026-14-7**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. and use of amides as **NK-1 receptor antagonists** against **benign prostatic hyperplasia**)

IT 123-90-0, Thiomorpholine 3282-30-2, Pivaloyl chloride 4548-45-2, 2-Chloro-5-nitropyridine 16419-60-6, o-Tolylboronic acid 139911-29-8, 4-Fluoro-2-methylphenylboronic acid 289686-69-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. and use of amides as **NK-1 receptor antagonists** against **benign prostatic hyperplasia**)

IT 219140-38-2P 471938-15-5P 474026-15-8P 474026-16-9P 474026-17-0P 474026-18-1P 474026-20-5P **474026-21-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and use of amides as **NK-1 receptor antagonists** against **benign prostatic hyperplasia**)

L116 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2003 ACS
AN **1999:753071** HCAPLUS
DN **131:346564**
TI Method using a **tachykinin** antagonist for treating or preventing chronic nonbacterial prostatitis and prostatodynia
IN Guess, Harry A.; Pearson, Jay Dee; Waldstreicher, Joanne
PA Merck & Co., Inc., USA
SO PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-40
ICS A61K031-535
CC 1-12 (Pharmacology)
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI WO 9959583 | A1 | 19991125 | WO 1999-US10736 | 19990514 |

W: AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,

CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9939938 A1 19991206 AU 1999-39938 19990514
US 6054455 A 20000425 US 1999-313002 19990517
PRAI US 1998-85866P P 19980518
WO 1999-US10736 W 19990514

AB A **tachykinin receptor antagonist**, in particular a **neurokinin-1 receptor antagonist**, is useful for the treatment or prevention of chronic nonbacterial prostatitis and/or prostatodynia.

ST **tachykinin receptor antagonist** nonbacterial prostatitis prostatodynia; **neurokinin 1 receptor antagonist** prostatitis prostatodynia

IT **Tachykinin receptors**
(**NK1** antagonists; **tachykinin** antagonist for treating or preventing chronic nonbacterial prostatitis and prostatodynia)

IT Antibiotics
(carbapenem; **tachykinin** antagonist and other agent for treating or preventing chronic nonbacterial prostatitis and prostatodynia)

IT Prostate-specific antigen
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(conjugates; **tachykinin** antagonist and other agent for treating or preventing chronic nonbacterial prostatitis and prostatodynia)

IT **Prostate gland**
(**disease**, prostatodynia; **tachykinin** antagonist for treating or preventing chronic nonbacterial prostatitis and prostatodynia)

IT Anti-inflammatory agents
(nonsteroidal; **tachykinin** antagonist and other agent for treating or preventing chronic nonbacterial prostatitis and prostatodynia)

IT **Prostate gland**
(prostatitis; **tachykinin** antagonist for treating or preventing chronic nonbacterial prostatitis and prostatodynia)

IT Cholinergic antagonists
(**tachykinin** antagonist and other agent for treating or preventing chronic nonbacterial prostatitis and prostatodynia)

IT **Tachykinin receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**tachykinin** antagonist for treating or preventing chronic nonbacterial prostatitis and prostatodynia)

IT Analgesics
(topical urinary; **tachykinin** antagonist and other agent for treating or preventing chronic nonbacterial prostatitis and prostatodynia)

IT Adrenoceptor antagonists
(.alpha.1-, .alpha.1a; **tachykinin** antagonist and other agent for treating or preventing chronic nonbacterial prostatitis and prostatodynia)

IT Adrenoceptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.alpha.1A, blockers; **tachykinin** antagonist and other agent for treating or preventing chronic nonbacterial prostatitis and prostatodynia)

IT 39391-18-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(2, inhibitors; **tachykinin** antagonist and other agent for treating or preventing chronic nonbacterial prostatitis and prostatodynia)

IT 83200-96-8D, Carbapenem, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antibiotics; **tachykinin** antagonist and other agent for treating or preventing chronic nonbacterial prostatitis and prostatodynia)
IT 9081-34-9, 5.alpha.-Reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; **tachykinin** antagonist and other agent for treating or preventing chronic nonbacterial prostatitis and prostatodynia)
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Bush; US 4822610 A 1989 HCAPLUS
(2) Gideon; US 5736144 A 1998
(3) Gormley; US 5629318 A 1997 HCAPLUS
(4) Oden; US 5580857 A 1996 HCAPLUS

L116 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2003 ACS
AN **1996:293223** HCAPLUS
DN **124:333868**
TI Pharmacological characterization of **tachykinin** NK2 **receptors** on isolated human urinary bladder, prostatic urethra and prostate
AU Palea, Stefano; Corsi, Mauro; Artibani, Walter; Ostardo, Edoardo; Pietra, Claudio
CS Dep. Pharmacol., Glaxo Res. Lab., Verona, Italy
SO Journal of Pharmacology and Experimental Therapeutics (1996), 277(2), 700-705
CODEN: JPETAB; ISSN: 0022-3565
PB Williams & Wilkins
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
AB The contractile effects of two highly potent, selective and peptidase-resistant **neurokinin** (**NK**) **1** and NK2 **receptor** agonists, namely GR 73632 and GR 64349, resp., were investigated on smooth muscle strips dissected from specimens of human detrusor, prostatic urethra and prostate. Furthermore, the potencies of two peptidic NK2 **receptor antagonists**, GR 87389 and L 659837, in **antagonizing** GR 64349-induced contractions were compared in these three tissues. In human detrusor muscle the rank order of agonist potency was: [.beta.-Ala8-NKA-(4-10)] > GR 64349 >> NKA-(4-10) >> substance P (SP) = GR 73632 >> SP Me ester. The NK2 **receptor antagonist**, GR 87389, **antagonized** GR 64349-induced contractions in a competitive manner, whereas L 659837 was a noncompetitive **antagonist**. In the prostatic urethra the rank order of agonist potency was GR 64349 > NKA-(4-10) > SP > GR 73632, whereas in the prostate it was: GR 64349 >> [.beta.-Ala8-NKA-(4-10)] > NKA-(4-10) > SP; GR 73632 was ineffective up to 30 .mu.M. In the prostatic urethra and in the prostate GR 87389 was a noncompetitive **antagonist** with a potency similar to that exhibited in the detrusor. On the contrary, L 659837 appeared to be a competitive **antagonist** in the prostate and in the prostatic urethra, having approx. the similar potency in these two tissues. The selective NK3 agonist senktide was ineffective up to 30 .mu.M in all three tissues. These results are discussed in the view of the proposed NK2 **receptor** subtypes and considering possible therapeutic implications in the treatment of urinary bladder disorders.
ST **tachykinin** NK2 **receptor** bladder urethra prostate
IT Bladder
**Prostate gland**

Urethra
(**tachykinin** NK2 **receptor** pharmacol. characterization in isolated human urinary bladder and prostatic urethra and prostate)

IT Kinin **receptors**
**Receptors**
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(**tachykinin** NK2, **tachykinin** NK2 **receptor** pharmacol. characterization in isolated human urinary bladder and prostatic urethra and prostate)

IT 33507-63-0, Substance P (peptide) 76260-78-1, Substance P methyl ester 97559-35-8, **Neurokinin** A-(4-10) 122063-01-8, .beta.-Ala8-**neurokinin** A(4-10) 133156-06-6, GR 73632 137593-52-3, GR 64349
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**tachykinin** NK2 **receptor** pharmacol. characterization in isolated human urinary bladder and prostatic urethra and prostate)

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L118 ANSWER 1 OF 12 HCAPLUS COPYRIGHT 2003 ACS
AN 2003:57902 HCAPLUS
DN 138:117662
TI Use of **NK-1 receptor antagonists** for the treatment of brain, spinal or nerve injury
IN **Hoffmann, Torsten**; Nimmo, Alan John; **Sleight, Andrew**; **Vankan, Pierre**; Vink, Robert
PA F. Hoffmann-La **Roche** A.-G., Switz.
SO PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-435
CC 1-11 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI WO 2003006016 | A2 | 20030123 | WO 2002-EP7323 | 20020703 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI EP 2001-116812 A 20010710
OS MARPAT 138:117662
AB The invention discloses the use of an **NK-1 receptor antagonist** (Markush included), e.g. N-(3,5-bis-trifluoromethylbenzyl)-N-methyl-6-(4-methylpiperazin-1-yl)-4-o-tolylnicotinamide, optionally in combination with a magnesium salt, for the treatment and/or prevention of brain, spinal or nerve injury. The invention also relates to pharmaceutical compns. comprising one or more such NK-1 **receptor antagonists**, optionally in combination with a magnesium salt, and a pharmaceutically acceptable

excipient, for the treatment and/or prevention of brain, spinal or nerve injury.

ST NK1 receptor antagonist brain spinal nerve injury; nicotinamide deriv NK1 antagonist brain spinal nerve injury

IT Drug delivery systems
(**NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury)

IT Cognition enhancers
(**NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury, and use with magnesium)

IT **Tachykinin receptors**
(**NK1 antagonists; NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury)

IT Mental disorder
(cognitive, cognitive function loss after brain injury; **NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury, and use with magnesium)

IT Cognition
(disorder, cognitive function loss after brain injury; **NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury, and use with magnesium)

IT Brain, disease
(edema; **NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury, and use with magnesium)

IT Brain, disease
Nerve, disease
Spinal cord
(injury; **NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury)

IT Behavior
(motor; **NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury, and use with magnesium)

IT Cytoprotective agents
(neuroprotectants; **NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury, and use with magnesium)

IT Biological transport
(permeation, blood-brain barrier post-traumatic permeability; **NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury, and use with magnesium)

IT Blood-brain barrier
(post-traumatic permeability; **NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury, and use with magnesium)

IT Drug delivery systems
(solns., injection; **NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury, and use with magnesium)

IT Brain, disease
(trauma; **NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury, and use with magnesium)

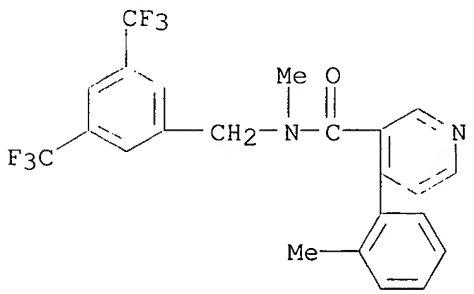
IT **290296-41-2 290296-42-3 290296-43-4**
**290296-44-5 290296-45-6 290296-46-7**
**290296-47-8 290296-49-0 290296-50-3**
**290296-51-4 290296-59-2 290296-66-1**
**290296-67-2 290296-68-3 290296-72-9**
**290296-73-0 290296-74-1 290296-75-2**
**290296-84-3 290296-85-4 290296-86-5**
**290296-87-6 290296-88-7 290296-89-8**
**290296-90-1 290296-91-2 290296-92-3**
**290296-93-4 290296-94-5 290296-95-6**
**290296-96-7 290296-98-9 290296-99-0**

290297-00-6 290297-01-7 290297-05-1
290297-18-6 290297-26-6 290297-30-2
290297-57-3 290297-58-4 290297-59-5
290297-61-9 290297-62-0 290297-63-1
290297-64-2 290297-65-3 290297-66-4
290298-21-4 391674-73-0 391674-74-1
391674-75-2 391674-76-3 391674-77-4
391674-78-5 391674-79-6 391674-80-9
391674-81-0 391674-82-1 391674-83-2
391674-84-3 391674-85-4 391674-86-5
391674-87-6 391674-89-8 391674-90-1
391674-91-2 391674-92-3 391674-93-4
391674-94-5 391674-95-6 391674-97-8
391674-98-9 391674-99-0 391675-00-6
391675-01-7 391675-02-8 393508-70-8
393508-71-9 393508-72-0 393508-73-1
393508-74-2 393508-75-3 393508-76-4
393508-77-5 393508-78-6 393508-79-7
393508-80-0 393508-81-1 393508-82-2
393508-84-4 393508-91-3 401891-32-5
401891-33-6 401891-34-7 401891-35-8
401891-36-9 401891-37-0 401891-38-1
401891-39-2 401891-40-5 401891-42-7
401891-43-8 401891-44-9 401891-45-0
401891-55-2 401891-63-2 401891-67-6
401891-70-1 401891-87-0 401891-90-5
401891-91-6 401891-94-9 401892-00-0
401892-10-2 401892-12-4 401892-24-8
401892-25-9 401892-29-3 401892-38-4
401892-63-5 474026-07-8 474026-11-4
474026-12-5 474026-13-6 488780-92-3
488780-93-4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury)

IT 7439-95-4, Magnesium, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury, and use with magnesium)

IT **290296-41-2**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**NK-1 receptor antagonist** for treatment of brain, spinal or nerve injury)

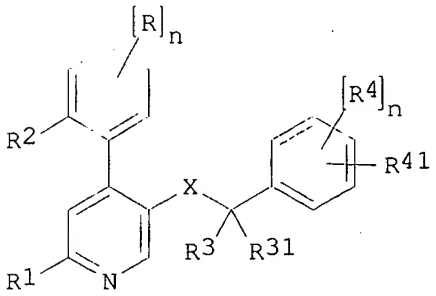
RN 290296-41-2 HCAPLUS
CN 3-Pyridinecarboxamide, N-[[3,5-bis(trifluoromethyl)phenyl]methyl]-N-methyl-4-(2-methylphenyl)- (9CI) (CA INDEX NAME)



L118 ANSWER 2 OF 12 HCAPLUS COPYRIGHT 2003 ACS
AN 2002:157739 HCAPLUS
DN 136:216651
TI Preparation of 4-phenylpyridines as **neurokinin-1 receptor antagonists**
IN Godel, Thierry; **Hoffmann, Torsten**; Schnider, Patrick; Stadler, Heinz
PA F. Hoffmann-La **Roche** A.-G., Switz.
SO PCT Int. Appl., 108 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D213-74
ICS C07D213-82; C07D213-79; C07D213-75; C07D413-04; C07D401-04; C07D409-04; C07D401-06; C07D401-12; C07D417-04; A61P025-00; A61P029-02; A61K031-4427; A61K031-455
CC 27-16 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 63
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 2002016324 | A1 | 20020228 | WO 2001-EP8686 | 20010727 <-- |
| | W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| | RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| | AU 2002012118 | A5 | 20020304 | AU 2002-12118 | 20010727 <-- |
| | US 2002040040 | A1 | 20020404 | US 2001-922066 | 20010803 <-- |
| PRAI | EP 2000-117003 | A | 20000808 <-- | | |
| | WO 2001-EP8686 | W | 20010727 | | |

OS MARPAT 136:216651
GI



I

AB The title compds. [I; R = H, halo; R1 = (C.tplbond.C)mR11, (CR'=CR'')mR11 (wherein R11 = halo, CN, aryl, etc.; R', R'' = H, OH, alkyl, etc.); R2 = H, alkyl, alkoxy, halo, CF3; R3, R31 = H, alkyl or form together with the C atom to which they are attached a cycloalkyl group; R4, R41 = H, halo, CF3, alkyl, alkoxy; R and R2 or R4 and R41 may be together CH=CHCH=CH, optionally substituted by one or two substituents selected from alkyl, halo or alkoxy; X = CONR8, (CH2)pO, (CH2)pNR8, NR8CO, NR8(CH2)p (wherein

R8 = H, alkyl); n = 1-2; m = 0-4; p = 1-2] which are **antagonists** of the **Neurokinin 1** (**NK-1**, substance P) **receptor**, and therefore useful in the treatment of diseases, related to this **receptor**, were prepd. and formulated. E.g., a multi-step synthesis of I [R = H; R1 = N(OH)CH2CH2OH; R2 = Me; R3, R31 = Me; R4 = 3-CF3; R41 = 5-CF3; X = NMeCO] which showed pKi of 9.29 in human NK1 **receptor** assay, was given.

ST phenylpyridine prepn formulation neurokinin NK1 antagonist; tachykinin NK1 antagonist phenylpyridine prepn formulation

IT **Tachykinin receptors**
(**NK1 antagonists**; prepn. of 4-phenylpyridines as **neurokinin-1 receptor antagonists**)

IT Human
(prepn. of 4-phenylpyridines as **neurokinin-1 receptor antagonists**)

IT **393508-84-4P 401891-34-7P 401891-36-9P**
**401891-37-0P 401891-41-6P 401891-47-2P**
**401891-48-3P 401891-49-4P 401891-53-0P**
**401891-54-1P 401891-55-2P 401891-56-3P**
**401891-58-5P 401891-59-6P 401891-60-9P**
**401891-63-2P 401891-66-5P 401891-67-6P**
**401891-69-8P 401891-78-9P 401891-80-3P**
401891-81-4P **401891-86-9P 401891-88-1P**
**401891-91-6P 401891-97-2P 401891-98-3P**
**401892-01-1P 401892-02-2P 401892-09-9P**
**401892-12-4P 401892-18-0P 401892-23-7P**
**401892-28-2P 401892-36-2P 401892-40-8P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of 4-phenylpyridines as **neurokinin-1 receptor antagonists**)

IT **393508-91-3P 401891-32-5P 401891-33-6P**
**401891-35-8P 401891-38-1P 401891-39-2P**
**401891-40-5P 401891-42-7P 401891-43-8P**
**401891-44-9P 401891-45-0P 401891-46-1P**
**401891-50-7P 401891-51-8P 401891-52-9P**
**401891-57-4P 401891-61-0P 401891-62-1P**
**401891-64-3P 401891-65-4P 401891-68-7P**
**401891-70-1P 401891-71-2P 401891-72-3P**
**401891-73-4P 401891-74-5P 401891-75-6P**
**401891-76-7P 401891-77-8P 401891-79-0P**
401891-82-5P **401891-83-6P** 401891-84-7P 401891-85-8P
**401891-87-0P 401891-89-2P 401891-90-5P**
**401891-92-7P 401891-93-8P 401891-94-9P**
**401891-95-0P 401891-96-1P 401891-99-4P**
**401892-00-0P 401892-03-3P 401892-04-4P**
**401892-05-5P 401892-06-6P 401892-07-7P**
**401892-08-8P 401892-10-2P 401892-11-3P**
**401892-13-5P 401892-14-6P 401892-15-7P**
**401892-16-8P 401892-17-9P 401892-19-1P**
**401892-20-4P 401892-21-5P 401892-22-6P**
**401892-24-8P 401892-25-9P 401892-26-0P**
**401892-27-1P 401892-29-3P 401892-30-6P**
**401892-31-7P 401892-32-8P 401892-33-9P**
**401892-34-0P 401892-35-1P 401892-37-3P**
**401892-38-4P 401892-39-5P 401892-41-9P**
**401892-42-0P 401892-43-1P 401892-44-2P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 4-phenylpyridines as **neurokinin-1**

**receptor antagonists**)

IT 60-56-0, 2-Mercapto-1-methylimidazole 66-25-1, Hexanal 75-65-0, tert-Butanol, reactions 98-17-9, 3-Hydroxybenzotrifluoride 100-39-0, Benzyl bromide 100-52-7, Benzaldehyde, reactions 108-03-2, 1-Nitropropane 109-75-1, Allylcyanide 110-91-8, Morpholine, reactions 140-67-0, 4-Allylanisole 541-41-3, Ethyl chloroformate 543-20-4, Succinyl chloride 591-50-4, Iodobenzene 627-32-7, 3-Iodopropanol 637-96-7, Sarcosine hydrochloride 693-98-1, 2-Methylimidazole 696-63-9, 4-Methoxythiophenol 762-62-9, 4,4-Dimethyl-1-pentene 765-30-0, Cyclopropylamine 767-00-0, 4-Hydroxybenzonitrile 872-85-5, 4-Pyridinecarboxaldehyde 873-55-2, Sodium benzenesulfinate 873-62-1, 3-Hydroxybenzonitrile 1066-54-2, Trimethylsilylacetylene 1692-15-5, 4-Pyridylboronic acid 1692-25-7, 3-Pyridylboronic acid 1765-93-1, 4-Fluorophenylboronic acid 2365-48-2, Methyl thioglycolate 2637-34-5, 2-Mercaptopyridine 2935-90-2, Methyl 3-mercaptopropionate 3282-30-2, Pivaloyl chloride 3678-63-5, 4-Chloro-2-methylpyridine 3900-89-8, 2-Chlorophenylboronic acid 4023-34-1, Cyclopropanecarboxylic acid chloride 4548-45-2, 2-Chloro-5-nitropyridine 4916-55-6, 3-(Bromomethyl)pyridine hydrobromide 5326-23-8, 6-Chloronicotinic acid 5720-06-9, 2-Methoxyphenylboronic acid 5720-07-0, 4-Methoxyphenylboronic acid 7051-34-5, (Bromomethyl)cyclopropane 7223-50-9, N-Propargylphthalimide 10365-98-7, 3-Methoxyphenylboronic acid 13472-85-0, 5-Bromo-2-methoxypyridine 13831-31-7, Acetoxyacetyl chloride 14763-60-1, 4-Methylsulfonylphenol 15570-12-4, 3-Methoxythiophenol 16114-47-9 16419-60-6, o-Tolylboronic acid 24854-43-1, 3-Mercapto-4-methyl-4H-1,2,4-triazole 32247-96-4, 3,5-Bis(trifluoromethyl)benzyl bromide 33872-80-9, o-Tolylmagnesium chloride 57260-71-6, 1-tert-Butoxycarbonylpiperazine 68337-15-5, 4-(1,2,4-Triazol-1-yl)phenol 73870-24-3, 4-(Bromomethyl)pyridine hydrobromide 75233-61-3, 2-(2-Nitroethoxy)tetrahydropyran 76782-82-6 97674-02-7, 1-Ethoxyvinyltributyltin 99768-12-4, 4-Methoxycarbonylphenylboronic acid 126747-14-6, 4-Cyanophenylboronic acid 139911-29-8, (4-Fluoro-2-methylphenyl)boronic acid 159820-24-3 168267-41-2, 3,4-Difluorophenylboronic acid 206551-43-1 286961-14-6 289686-69-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of 4-phenylpyridines as **neurokinin-1 receptor antagonists**)

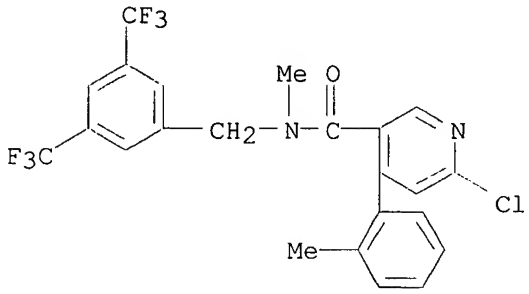
IT 22282-65-1P 26820-62-2P 52023-68-4P 53939-30-3P, 5-Bromo-2-chloropyridine 54189-82-1P, 6-Chloro-N-methylnicotinamide **290296-68-3P 290296-83-2P 290296-89-8P 290296-93-4P 290297-13-1P 290297-14-2P** 290297-32-4P 290297-33-5P 290297-34-6P 290297-35-7P 290297-36-8P 290297-39-1P 290297-40-4P **290297-41-5P** 290297-53-9P 290298-22-5P 342416-98-2P **391674-73-0P 391674-74-1P 393508-76-4P 401892-45-3P 401892-46-4P** 401892-47-5P 401892-48-6P 401892-49-7P 401892-50-0P 401892-51-1P 401892-52-2P 401892-53-3P 401892-54-4P 401892-55-5P **401892-56-6P 401892-57-7P 401892-58-8P 401892-59-9P 401892-60-2P 401892-61-3P 401892-62-4P 401892-63-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of 4-phenylpyridines as **neurokinin-1 receptor antagonists**)

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Grugn; WO 9719926 A 1997 HCAPLUS
(2) Hoffmann La Roche; WO 0050398 A 2000 HCAPLUS
(3) Hoffmann La Roche; EP 1035115 A 2000 HCAPLUS
(4) Hoffmann La Roche; EP 1103545 A 2001 HCAPLUS
(5) Ikeura, Y; CHEMICAL AND PHARMACEUTICAL BULLETIN 1997, V45(10), P1642 HCAPLUS

IT **393508-84-4P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of 4-phenylpyridines as **neurokinin-1 receptor antagonists**)
RN 393508-84-4 HCAPLUS
CN 3-Pyridinecarboxamide, N-[[3,5-bis(trifluoromethyl)phenyl]methyl]-6-chloro-N-methyl-4-(2-methylphenyl)- (9CI) (CA INDEX NAME)




L118 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2003 ACS
AN 2002:90050 HCAPLUS
DN 136:134681
TI Preparation of 4-phenylpyridine derivatives as **neurokinin-1 receptor antagonists**
IN **Hoffmann, Torsten**; Schnider, Patrick; Stadler, Heinz
PA F. Hoffmann-La **Roche** A.-G., Switz.
SO PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D521-00
ICS C07D213-82; C07D401-04; C07D213-75; C07D413-04; A61K031-4427; A61K031-465; A61P025-00; A61P029-00
CC 27-16 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 63
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 2002008232 | A1 | 20020131 | WO 2001-EP8432 | 20010720 <-- |
| | W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| | RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| | US 2002038030 | A1 | 20020328 | US 2001-901311 | 20010709 <-- |
| PRAI | EP 2000-115846 | A | 20000724 <-- | | |

OS MARPAT 136:134681
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. [I or II; R1 = III, 2,3-dihydro-[1,4]oxazin-4-yl, imidazol-1-yl, [1,2,4]triazol-1-yl, NH(CH2)2OH, NR3COCH3, NR3COcyclopropyl; R2 = Me, Cl; R3 = H, Me; R = H, (CH2)2OH; n = 1-2] which have a good affinity of the NK-1 receptor and therefore they may be used in the treatment or prevention of diseases, related to this receptor, were prepd. and formulated. E.g., a multi-step synthesis of I [R1 = [1,2,4]triazol-1-yl; R2 = Me] which showed pKi of 8.4 against binding at human NK1 receptors in CHO cells, was given.

ST phenylpyridine prepn neurokinin NK1 receptor antagonist

IT Human
(prepn. of 4-phenylpyridines as **neurokinin-1 receptor antagonists**)

IT **Tachykinin receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**type NK1**; prepn. of 4-phenylpyridines as **neurokinin-1 receptor antagonists**)

IT **393508-72-0P 393508-79-7P 393508-81-1P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of 4-phenylpyridines as **neurokinin-1 receptor antagonists**)

IT **393508-70-8P 393508-71-9P 393508-73-1P**
**393508-74-2P 393508-75-3P 393508-76-4P**
**393508-77-5P 393508-78-6P 393508-80-0P**
**393508-82-2P 393508-83-3P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 4-phenylpyridines as **neurokinin-1 receptor antagonists**)

IT 110-91-8, Morpholine, reactions 288-32-4, Imidazole, reactions 288-88-0, 1H-1,2,4-Triazole 2799-21-5 3282-30-2, Pivaloyl chloride 3900-89-8, 2-Chlorophenylboronic acid 4023-34-1, Cyclopropanecarboxylic acid chloride 4548-45-2, 2-Chloro-5-nitropyridine 5326-23-8, 6-Chloronicotinic acid 5382-16-1, 4-Hydroxypiperidine 16419-60-6, o-Tolylboronic acid 32247-96-4, 3,5-Bis(trifluoromethyl)benzyl bromide 33872-80-9, o-Tolylmagnesium chloride 86864-60-0 289686-69-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of 4-phenylpyridines as **neurokinin-1 receptor antagonists**)

IT 26820-62-2P 52023-68-4P 54189-82-1P **290296-68-3P**
**290297-13-1P 290297-14-2P** 290297-32-4P 290297-33-5P
290297-34-6P 290297-35-7P 290297-36-8P 290297-40-4P
**290297-41-5P** 290298-22-5P 342416-98-2P **393508-84-4P**
**393508-85-5P** 393508-86-6P 393508-87-7P 393508-88-8P
393508-89-9P **393508-90-2P 393508-91-3P**
**393508-92-4P** 393508-93-5P **393509-29-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of 4-phenylpyridines as **neurokinin-1 receptor antagonists**)

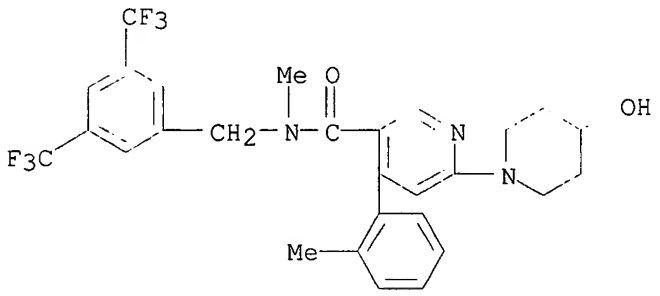
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Hoffmann La Roche; DE 10008042 A 2000 HCAPLUS
(2) Hosoki, R; EUROPEAN JOURNAL OF PHARMACOLOGY 1998, V341(2/3), P235 HCAPLUS
(3) Ikeura, Y; CHEMICAL AND PHARMACEUTICAL BULLETIN 1997, V45(10), P1642 HCAPLUS
(4) Natsugari, H; WO 9947132 A 1999 HCAPLUS
(5) Natsugari, H; JOURNAL OF MEDICINAL CHEMISTRY 1995, V38(16), P3106 HCAPLUS

IT **393508-72-0P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic

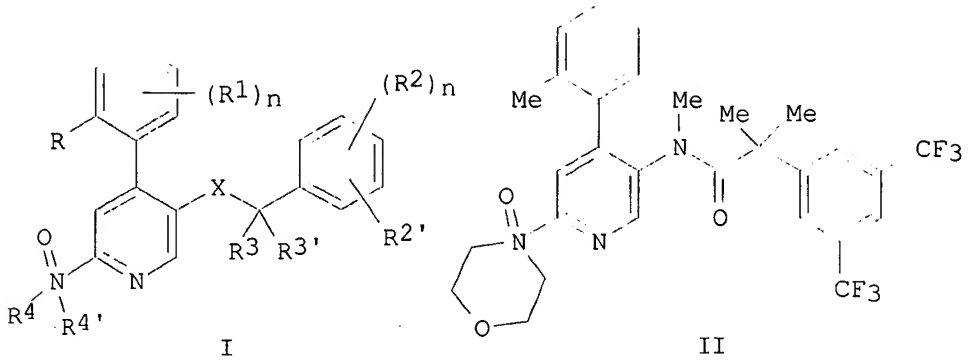
preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of 4-phenylpyridines as **neurokinin-1 receptor antagonists**)
RN 393508-72-0 HCAPLUS
CN 3-Pyridinecarboxamide, N-[[3,5-bis(trifluoromethyl)phenyl]methyl]-6-(4-hydroxy-1-piperidinyl)-N-methyl-4-(2-methylphenyl)- (9CI) (CA INDEX NAME)




L118 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2003 ACS
AN 2002:72051 HCAPLUS
DN 136:118387
TI Preparation of N-oxides as NK1 receptor antagonist prodrugs of 4-phenylpyridine derivatives
IN **Hoffmann, Torsten**; Poli, Sonia Maria; Schnider, Patrick; **Sleight, Andrew**
PA F. Hoffmann-La **Roche** A.-G., Switz.
SO PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D213-76
ICS C07D213-82; C07D401-04; A61K031-44; A61P025-22; A61P025-24
CC 27-16 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 63
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 2002006236 | A1 | 20020124 | WO 2001-EP7850 | 20010709 <-- |
| | W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| | RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| | US 2002045642 | A1 | 20020418 | US 2001-904059 | 20010712 <-- |
| PRAI | EP 2000-115287 | A | 20000714 <-- | | |

OS MARPAT 136:118387
GI



I II

AB The prepn. is described for N-oxides (I) wherein R is hydrogen, lower alkyl, lower alkoxy, or trifluoromethyl; R1 is hydrogen or halogen; or R and R1 may be together with the ring carbon atoms to which they are attached -CH=CH-CH=CH-; R2 and R2' are independently from each other hydrogen, halogen, trifluoromethyl, lower alkoxy or cyano; or R2 and R2' may be together -CH=CH-CH=CH-, optionally substituted by one or two substituents selected from lower alkyl or lower alkoxy; R3, R3' are independently from each other hydrogen, lower alkyl or cycloalkyl; R4, R4' are independently from each other -(CH2)mOR6 or lower alkyl; or R4 and R4' form together with the N-atom to which they are attached a cyclic tertiary amine with substituent R5 chosen from hydrogen, hydroxy, lower alkyl, -lower alkoxy, -(CH2)mOH, -COOR3, -CON(R3)2,-N(R3)CO-lower alkyl or -C(O)R3; R6 is hydrogen, lower alkyl or phenyl; X is -C(O)N(R6)-, -N(R6)C(O)-, -(CH2)mO- or -O(CH2)m-; n is 0, 1, 2, 3 or 4 and; m is 1, 2, or 3; and to their pharmaceutically acceptable acid addn. salts. These compds. may be uses as prodrugs for the treatment or prevention of illnesses, related to the NK1 receptor. Thus, 2-[3,5-bis(trifluoromethyl)phenyl]-N-methyl-N-[6-(4-oxymorpholin-4-yl)-4-o-tolylpyridin-3-yl]isobutyramide (II) and related compds. were prepd. in multistep procedures.

ST aminopyridine oxide prepn NK1 receptor antagonist prodrug; oxymorpholinylpyridine prepn NK1 receptor antagonist prodrug

IT **Tachykinin receptors**
(**NK1 antagonists**; prepn. of N-oxides as **NK1** receptor antagonist prodrugs of 4-phenylpyridine derivs.)

IT 26820-62-2P 52023-68-4P 54189-82-1P **290296-68-3P**
**290296-70-7P 290296-71-8P 290296-73-0P**
**290296-74-1P 290296-75-2P 290296-76-3P**
**290296-77-4P 290296-83-2P 290296-85-4P**
**290296-87-6P 290296-89-8P 290296-90-1P**
**290296-91-2P 290296-92-3P 290297-00-6P**
**290297-01-7P 290297-02-8P 290297-03-9P**
**290297-04-0P 290297-05-1P 290297-06-2P**
**290297-07-3P 290297-08-4P 290297-10-8P**
**290297-11-9P** 290297-32-4P 290297-33-5P 290297-34-6P
290297-35-7P 290297-36-8P 290297-39-1P 290297-53-9P
**290298-21-4P** 342416-98-2P **391675-02-8P**
**391675-03-9P 391675-11-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate product in prepn. of aminopyridine N-oxides as NK1 receptor antagonist prodrugs of 4-phenylpyridine derivs.)

IT **391674-73-0P 391674-74-1P 391674-75-2P**
**391674-76-3P 391674-77-4P 391674-78-5P**
**391674-79-6P 391674-80-9P 391674-81-0P**
**391674-82-1P 391674-83-2P 391674-84-3P**

**391674-85-4P 391674-86-5P 391674-87-6P**
**391674-88-7P 391674-89-8P 391674-90-1P**
**391674-91-2P 391674-92-3P 391674-93-4P**
**391674-94-5P 391674-95-6P 391674-96-7P**
**391674-97-8P 391674-98-9P 391674-99-0P**
**391675-00-6P 391675-01-7P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of aminopyridine N-oxides as NK1 receptor antagonist prodrugs of 4-phenylpyridine derivs.)

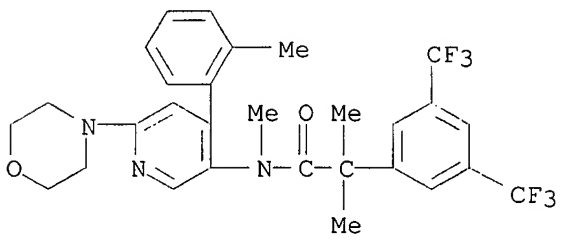
IT 79286-87-6, 3-(Acetylmethylamino)pyrrolidine
RL: RCT (Reactant); RACT (Reactant or reagent)
(racemic; reactant for prepn. of aminopyridine N-oxides as NK1 receptor antagonist prodrugs of 4-phenylpyridine derivs.)

IT 86-52-2, 1-(Chloromethyl)naphthalene 109-83-1, N-Methylethanolamine 110-89-4, Piperidine, reactions 110-91-8, Morpholine, reactions 123-90-0, Thiomorpholine 506-59-2, Dimethylamine hydrochloride 1126-09-6, Ethyl isonipecotate 1765-40-8, 2,3,4,5,6-Pentafluorobenzyl bromide 2799-21-5, (R)-3-Hydroxypyrrolidine 2942-59-8, 2-Chloronicotinic acid 3771-13-9, 2-Chloro-5-methoxybenzyl bromide 3900-89-8, 2-Chlorophenylboronic acid 4548-45-2, 2-Chloro-5-nitropyridine 4670-10-4, 3,5-Dimethoxyphenylacetic acid 5382-16-1, 4-Hydroxypiperidine 6626-23-9, 1-(Chloromethyl)-2-methylnaphthalene 7035-02-1, 2-Methoxybenzyl chloride 7035-11-2, 5-Chloro-2-methoxybenzyl chloride 16419-60-6, o-Tolylboronic acid 32247-96-4, 3,5-Bis(trifluoromethyl)benzyl bromide 33872-80-9, o-Tolylmagnesium chloride 57260-71-6, 1-tert-Butoxycarbonylpiperazine 85068-33-3, 3,5-Bis(trifluoromethyl)phenylacetic acid 86802-98-4, 2-(Chloromethyl)-1,4-dimethoxynaphthalene 195447-79-1, 3-Fluoro-5-(trifluoromethyl)phenylacetic acid 289686-69-7
**290296-93-4** 290297-55-1 391675-13-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant for prepn. of aminopyridine N-oxides as NK1 receptor antagonist prodrugs of 4-phenylpyridine derivs.)

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) F Hoffmann-La Roche Ag; EP 1035115 A 2000 HCAPLUS
(2) F Hoffmann-La Roche Ag; EP 1103545 A 2001 HCAPLUS
(3) Ikeura, Y; CHEM PHARM BULL 1997, V45(10), P1642 HCAPLUS

IT **290296-68-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate product in prepn. of aminopyridine N-oxides as NK1 receptor antagonist prodrugs of 4-phenylpyridine derivs.)

RN 290296-68-3 HCAPLUS
CN Benzeneacetamide, N,.alpha.,.alpha.-trimethyl-N-[4-(2-methylphenyl)-6-(4-morpholinyl)-3-pyridinyl]-3,5-bis(trifluoromethyl)- (9CI) (CA INDEX NAME)

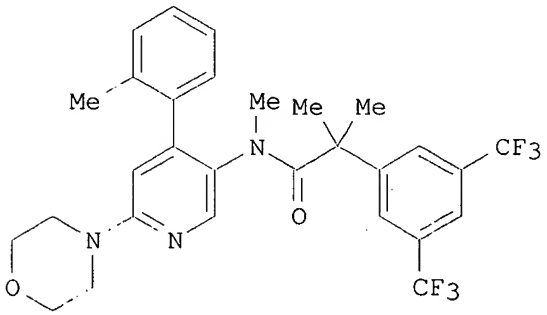



L118 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2003 ACS
AN 2001:396484 HCAPLUS

DN 135:5620
TI Preparation of 2-[3,5-bis(trifluoromethyl)phenyl]-N-methyl-N-[6-(morpholin-4-yl)-4-(o-tolyl)-pyridin-3-yl]-isobutyramide for the treatment of diseases related to the NK-1 receptor
IN Ballard, Theresa Maria; Higgins, Guy Andrew; **Hoffmann, Torsten**; Poli, Sonia Maria; **Sleight, Andrew**
PA F. Hoffmann-La **Roche** A.-G., Switz.
SO Eur. Pat. Appl., 12 pp.
CODEN: EPXXDW
DT Patent
LA English
IC ICM C07D213-75
ICS A61K031-44; A61P025-22; A61P025-24
CC 28-13 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | EP 1103545 | A1 | 20010530 | EP 2000-125450 | 20001121 <-- |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| | GB 2356863 | A1 | 20010606 | GB 2000-28566 | 20001123 <-- |
| | DE 10058310 | A1 | 20010531 | DE 2000-10058310 | 20001124 <-- |
| | FR 2801590 | A1 | 20010601 | FR 2000-15193 | 20001124 <-- |
| | JP 2001151754 | A2 | 20010605 | JP 2000-356833 | 20001124 <-- |
| | NO 2000006012 | A | 20010530 | NO 2000-6012 | 20001128 <-- |
| | BR 2000005616 | A | 20010717 | BR 2000-5616 | 20001128 <-- |
| | ES 2171134 | A1 | 20020816 | ES 2000-2839 | 20001128 <-- |
| | CN 1297888 | A | 20010606 | CN 2000-134260 | 20001129 <-- |
| PRAI | EP 1999-123685 | A | 19991129 <-- | | |

GI




I

AB The title compd. I which is a potent and selective antagonist at recombinant human neurokinin1 (NK1) receptors expressed in CHO cells, was prepd. (details of multi-step synthesis were given) and formulated. The compd. I showed an affinity (pKi) of 9.0 for the human NK1 receptor over 2 orders of magnitude of selectivity for the NK1 receptor compared to NK2 and NK3 receptors and compared to over 50 other binding sites that have been evaluated.
ST neurokinin receptor selective antagonist bistrifluoromethylphenylmethylmorpholinyltolylpyridinylisobutyramide
IT **Tachykinin receptors**
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(**NK1**; prepn. of 2-[3,5-bis(trifluoromethyl)phenyl]-N-methyl-N-[6-(morpholin-4-yl)-4-(o-tolyl)-pyridin-3-yl]-isobutyramide for the treatment of diseases related to the NK-1 receptor)
IT **290296-68-3P 341023-51-6P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 2-[3,5-bis(trifluoromethyl)phenyl]-N-methyl-N-[6-(morpholin-4-yl)-4-(o-tolyl)-pyridin-3-yl]-isobutyramide for the treatment of diseases related to the NK-1 receptor)

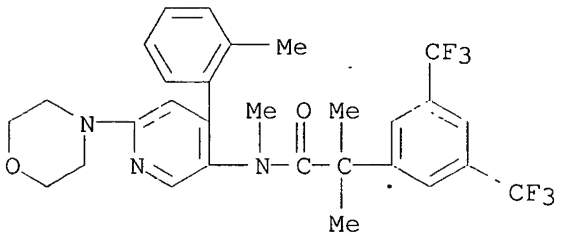
IT 110-91-8, Morpholine, reactions 3282-30-2, Pivaloyl chloride 4548-45-2, 2-Chloro-5-nitropyridine 16419-60-6, o-Tolylboronic acid 289686-69-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of 2-[3,5-bis(trifluoromethyl)phenyl]-N-methyl-N-[6-(morpholin-4-yl)-4-(o-tolyl)-pyridin-3-yl]-isobutyramide for the treatment of diseases related to the NK-1 receptor)

IT 26820-62-2P 52023-68-4P 290297-32-4P 290297-33-5P 290297-34-6P 290297-35-7P 290297-36-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of 2-[3,5-bis(trifluoromethyl)phenyl]-N-methyl-N-[6-(morpholin-4-yl)-4-(o-tolyl)-pyridin-3-yl]-isobutyramide for the treatment of diseases related to the NK-1 receptor)

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Glaxo Group Ltd; EP 0916346 A 1999 HCAPLUS
(2) La Roche, H; EP 1035115 A 2000 HCAPLUS

IT **290296-68-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 2-[3,5-bis(trifluoromethyl)phenyl]-N-methyl-N-[6-(morpholin-4-yl)-4-(o-tolyl)-pyridin-3-yl]-isobutyramide for the treatment of diseases related to the NK-1 receptor)

RN 290296-68-3 HCAPLUS
CN Benzeneacetamide, N,.alpha.,.alpha.-trimethyl-N-[4-(2-methylphenyl)-6-(4-morpholinyl)-3-pyridinyl]-3,5-bis(trifluoromethyl)- (9CI) (CA INDEX NAME)




L118 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2003 ACS
AN 2000:607348 HCAPLUS
DN 133:207811
TI Preparation of N-benzyl-4-tolylnicotinamides and related compounds as **neurokinin-1 receptor antagonists.**
IN Boes, Michael; Branca, Quirico; Galley, Guido; Godel, Thierry; **Hoffmann, Torsten**; Hunkeler, Walter; Schnider, Patrick; Stadler, Heinz
PA F. Hoffmann-La **Roche** Ag, Switz.
SO Ger. Offen., 38 pp.
CODEN: GWXXBX
DT Patent
LA German
IC ICM C07D213-82
ICS C07D213-36; C07D213-22; C07D401-02; A61K031-4406
CC 27-16 (Heterocyclic Compounds (One Hetero Atom))

Section cross-reference(s): 1, 28

FAN.CNT 3

| | PATENT NO. | KIND | DATE | | APPLICATION NO. | DATE | |
|---|---|---|---|---|---|---|---|
| PI | DE 10008042 | A1 | 20000831 | | DE 2000-10008042 | 20000222 | <-- |
| | EP 1035115 | A1 | 20000913 | | EP 2000-102260 | 20000215 | <-- |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | | | |
| | GB 2347422 | A1 | 20000906 | | GB 2000-3908 | 20000218 | <-- |
| | FR 2790473 | A1 | 20000908 | | FR 2000-2170 | 20000222 | <-- |
| | US 6297375 | B1 | 20011002 | | US 2000-507456 | 20000222 | <-- |
| | ZA 2000000894 | A | 20000824 | | ZA 2000-894 | 20000223 | <-- |
| | NO 2000000885 | A | 20000825 | | NO 2000-885 | 20000223 | <-- |
| | BR 2000000908 | A | 20000912 | | BR 2000-908 | 20000223 | <-- |
| | CN 1270959 | A | 20001025 | | CN 2000-102401 | 20000223 | <-- |
| | ES 2171109 | A1 | 20020816 | | ES 2000-418 | 20000223 | <-- |
| | JP 2000247957 | A2 | 20000912 | | JP 2000-47003 | 20000224 | <-- |
| | US 2002091265 | A1 | 20020711 | | US 2001-901982 | 20010710 | <-- |
| | US 6479483 | B2 | 20021112 | | | | |
| PRAI | EP 1999-103504 | A | 19990224 | <-- | | | |
| | EP 1999-123689 | A | 19991129 | <-- | | | |
| | US 2000-507456 | A3 | 20000222 | <-- | | | |

OS MARPAT 133:207811

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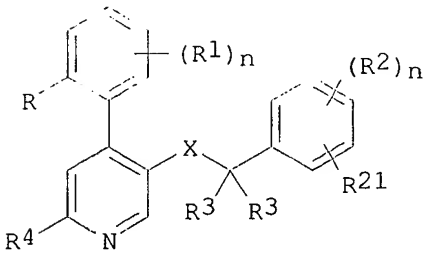


I

AB Title compds. [I; R = H, alkyl, alkoxy, halo, CF3; R1 = H, halo; RR1 = CH:CHCH:CH; R2, R21 = H, halo, CF3, alkoxy, cyano; R2R21 = (substituted) CH:CHCH:CH; R3 = H, alkyl, cycloalkyl; R4 = H, N(R5)2, N(R5)(CH2)nOH, N(R5)S(O)2A, N(R5)S(O)2Ph, N:CHN(R5)2, N(R5)C(O)R5, specified cyclic tertiary amine; R5 = H, cycloalkyl, benzyl, alkyl; X = C(O)N(R5), (CH2)mO, (CH2)mN(R5), N(R5)C(O), N(R5)(CH2)m; n = 0-4; m = 1, 2], were prepd. Thus, 4-o-tolylnicotinic acid (prepn. given) was stirred with SOCl2 and cat. DMF in CH2Cl2 to give a residue which was refluxed with N-[3,5-bis(trifluoromethyl)benzyl]-N-methylamine and Et3N in PhMe to give 67% N-(3,5-bistrifluoromethylbenzyl)-N-methyl-4-o-tolylnicotinamide. Tested I **antagonized NK-1 receptors** with pKi = 8.20-9.54.

ST benzyltolylnicotinamide prepn neurokinin antagonist; nicotinamide benzyl tolyl prepn neurokinin antagonist

IT **Tachykinin receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(**NK1, antagonists**; prepn. of N-benzyl-4-tolylnicotinamides and related compds. as **neurokinin-1 receptor antagonists**)

IT **290297-14-2P 290297-18-6P 290297-26-6P 290297-30-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of N-benzyl-4-tolylnicotinamides and related compds. as **neurokinin-1 receptor antagonists**
)

IT **290296-41-2P 290296-42-3P 290296-43-4P**
**290296-44-5P 290296-45-6P 290296-46-7P**
**290296-47-8P 290296-48-9P 290296-49-0P**
**290296-50-3P 290296-51-4P 290296-52-5P**
**290296-53-6P 290296-54-7P 290296-55-8P**
**290296-56-9P 290296-57-0P 290296-58-1P**
**290296-59-2P 290296-60-5P 290296-61-6P**
**290296-62-7P 290296-63-8P 290296-65-0P**
**290296-66-1P 290296-67-2P 290296-68-3P**
**290296-69-4P 290296-70-7P 290296-71-8P**
**290296-72-9P 290296-73-0P 290296-74-1P**
**290296-75-2P 290296-76-3P 290296-77-4P**
**290296-78-5P 290296-79-6P 290296-80-9P**
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**290297-03-9P 290297-04-0P 290297-05-1P**
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**290297-09-5P 290297-10-8P 290297-11-9P**
**290297-12-0P 290297-13-1P 290297-15-3P**
**290297-16-4P 290297-17-5P 290297-57-3P**
**290297-58-4P 290297-59-5P 290297-60-8P**
**290297-61-9P 290297-62-0P 290297-63-1P**
**290297-64-2P 290297-65-3P 290297-66-4P**
**290298-21-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-benzyl-4-tolylnicotinamides and related compds. as **neurokinin-1 receptor antagonists**
)

IT 86-52-2, 1-Chloromethylnaphthalene 98-09-9, Benzenesulfonyl chloride 98-80-6, Phenylboronic acid 107-14-2, Chloroacetonitrile 109-01-3, 1-Methylpiperazine 109-83-1, N-Methylethanolamine 110-91-8, Morpholine, reactions 123-90-0, Thiomorpholine 124-63-0, Methanesulfonyl chloride 501-53-1 540-51-2, 2-Bromoethanol 628-89-7, 2-(2-Chloroethoxy)ethanol 653-35-0, 2,3,4,5,6-Pentafluorobenzyl chloride 1126-09-6, Ethyl isonipecotate 1423-27-4 1993-03-9 2506-41-4, 2-Chloromethylnaphthalene 2799-21-5 2942-59-8, 2-Chloronicotinic acid 3900-89-8 4548-45-2, 2-Chloro-5-nitropyridine 4670-10-4, 3,5-Dimethoxyphenylacetic acid 5382-16-1, 4-Hydroxypiperidine 5720-06-9, o-Methoxyphenylboronic acid 6626-23-9, 1-Chloromethyl-2-methylnaphthalene 7035-02-1, 2-Methoxybenzyl chloride 7035-11-2, 5-Chloro-2-methoxybenzyl chloride 16419-60-6, o-Tolylboronic acid 20980-22-7, 2-(1-Piperazinyl)pyrimidine 21867-64-1, 1-Propylpiperazine 32247-96-4 33872-80-9, o-Tolylmagnesium chloride 40004-08-8, 1-Ethoxycarbonylmethylpiperazine 41239-40-1 50893-53-3 51791-12-9, 3-Chloromethyl-1,2,4-oxadiazole 57260-71-6, 1-tert-Butoxycarbonylpiperazine 63592-85-8, Methyl 4-chloronicotinate 70298-88-3 79286-87-6 85068-33-3 86802-98-4 90390-21-9 90390-28-6 101079-83-8, 2-Chloro-5-methoxybenzyl chloride 139911-29-8, 4-Fluoro-2-methylphenylboronic acid 155742-64-6 159820-24-3 195447-79-1 201345-08-6 289686-69-7 290297-42-6 290297-43-7

290297-44-8 290297-45-9 290297-46-0 **290297-47-1**
290297-48-2 290297-49-3 290297-50-6 290297-51-7 290297-52-8
290297-53-9 290297-54-0 290297-55-1 290297-56-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of N-benzyl-4-tolylnicotinamides and related compds. as **neurokinin-1 receptor antagonists**
)

IT 26820-62-2P 54189-82-1P 54864-91-4P 55403-34-4P 105812-87-1P
113975-32-9P 207850-76-8P 290297-19-7P 290297-20-0P 290297-21-1P
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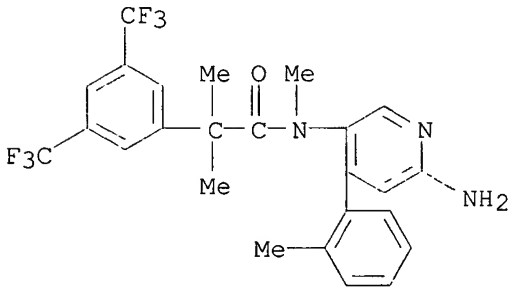
290297-33-5P 290297-34-6P 290297-35-7P 290297-36-8P 290297-37-9P
290297-38-0P 290297-39-1P 290297-40-4P **290297-41-5P**
290298-22-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of N-benzyl-4-tolylnicotinamides and related compds. as **neurokinin-1 receptor antagonists**
)

IT **290297-14-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of N-benzyl-4-tolylnicotinamides and related compds. as **neurokinin-1 receptor antagonists**
)

RN 290297-14-2 HCAPLUS
CN Benzeneacetamide, N-[6-amino-4-(2-methylphenyl)-3-pyridinyl]-N,.alpha.,.alpha.-trimethyl-3,5-bis(trifluoromethyl)- (9CI) (CA INDEX NAME)




L118 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2003 ACS
AN 1999:613656 HCAPLUS
DN 131:228734
TI Preparation of diazocinonaphthyridines, diazepinonaphthyridines, and related compounds having tachykinin receptor antagonistic activity for preventing or treating depression, anxiety, manic-depressive illness or psychopathy.
IN Natsugari, Hideaki; Doi, Takayuki; Ikeura, Yoshinori
PA Takeda Chemical Industries, Ltd., Japan
SO PCT Int. Appl., 207 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-00
CC 28-23 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63
FAN.CNT 1

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| | RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | | | |
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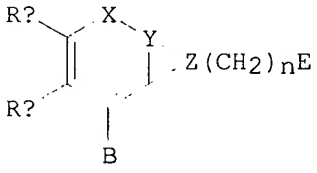
| PRAI | JP 1998-69999 | A | 19980319 | <-- | | | |
| | EP 1999-909233 | A3 | 19990318 | <-- | | | |
| | WO 1999-JP1358 | W | 19990318 | <-- | | | |
| | US 1999-308311 | A1 | 19990518 | <-- | | | |

OS MARPAT 131:228734

GI




I

AB Pharmaceutical compns. for preventing or treating depression, anxiety, manic-depression, or psychopathy [I; XY = N:C, CON, CSN; Ra, Rb = H, substituent; RaRb = atoms to form a (substituted) (heterocyclic) ring; B, E = (substituted) homocyclic or heterocyclic ring, Z = (substituted) N-contg. heterocyclic ring; n = 1-6; with provisos], are claimed. Thus, (9R)-7-[3,5-bis(trifluoromethyl)benzyl]-6,7,8,9,10,11-hexahydro-9-methyl-5-(4-methylphenyl)-6,13-dioxo-13H-[1,4]-diazocino[2,1-g][1,7]naphthyridine (II) (prepn. described) antagonized substance P with IC50 = 0.43 nM. A II tablet formulation is given.

ST diazocinonaphthyridine diazepinonaphthyridine prepn tachykinin receptor antagonist; arthritis treatment diazocinonaphthyridine diazepinonaphthyridine; pain treatment diazocinonaphthyridine diazepinonaphthyridine; cough treatment diazocinonaphthyridine diazepinonaphthyridine; psychopathy treatment diazocinonaphthyridine diazepinonaphthyridine; anxiety treatment diazocinonaphthyridine diazepinonaphthyridine; depression treatment diazocinonaphthyridine diazepinonaphthyridine

IT **Tachykinin receptors**

RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)

(antagonists; prepn. of diazocinonaphthyridines, diazepinonaphthyridines, and related compds. having tachykinin receptor

antagonistic activity)

IT Intestine, disease
(irritable bowel syndrome, treatment; prepn. of diazocinonaphthyridines, diazepinonaphthyridines, and related compds. having tachykinin receptor antagonistic activity)

IT Mental disorder
(manic bipolar disorder, treatment; prepn. of diazocinonaphthyridines, diazepinonaphthyridines, and related compds. having tachykinin receptor antagonistic activity)

IT Analgesics
Antiarthritics
Antiasthmatics
Antidepressants
Antiemetics
Antipsychotics
Antitussives
Anxiolytics
(prepn. of diazocinonaphthyridines, diazepinonaphthyridines, and related compds. having tachykinin receptor antagonistic activity)

IT 33507-63-0, Substance P **86933-74-6**, Neurokinin A
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(antagonists; prepn. of diazocinonaphthyridines, diazepinonaphthyridines, and related compds. having tachykinin receptor antagonistic activity)

IT 207606-22-2P 207606-26-6P
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of diazocinonaphthyridines, diazepinonaphthyridines, and related compds. having tachykinin receptor antagonistic activity)

IT 183145-60-0P 183549-77-1P 183549-78-2P 183549-79-3P 183549-80-6P
183549-81-7P 183549-82-8P 183549-83-9P 183549-84-0P 183549-85-1P
183549-86-2P 183549-87-3P 183549-88-4P 183549-89-5P 183549-90-8P
183549-91-9P 183549-92-0P 183549-93-1P 183549-94-2P 183549-95-3P
183549-96-4P 183549-97-5P 183549-98-6P 183550-00-7P 183550-02-9P
183550-03-0P 183550-05-2P 183550-07-4P 183550-08-5P 183550-09-6P
183550-10-9P 183550-11-0P 183550-13-2P 183550-15-4P 183550-16-5P
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183550-27-8P 183550-29-0P 183550-31-4P 183550-32-5P 183550-33-6P
183550-34-7P 183550-35-8P 183550-36-9P 183550-37-0P 183550-38-1P
183550-39-2P 183550-40-5P 183550-41-6P 183550-42-7P 183550-43-8P
183550-44-9P 183550-45-0P 183550-46-1P 183550-47-2P 183550-48-3P
183550-49-4P 183550-50-7P 183550-51-8P 183550-52-9P 183550-53-0P
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244107-02-6P 244107-03-7P 244107-04-8P 244107-05-9P 244107-06-0P

244107-07-1P 244107-08-2P 244107-09-3P 244107-10-6P 244107-11-7P
244107-12-8P 244107-13-9P 244107-14-0P 244107-15-1P 244107-16-2P
244107-17-3P 244107-18-4P 244107-25-3P 244107-42-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of diazocinonaphthyridines, diazepinonaphthyridines, and related compds. having tachykinin receptor antagonistic activity)

IT 67-63-0, Isopropanol, reactions 74-89-5, Methylamine, reactions 74-93-1, Methyl mercaptan, reactions 100-46-9, Benzylamine, reactions 102-49-8, 3,4-Dichlorobenzylamine 104-63-2 106-38-7, 4-Bromotoluene 108-24-7, Acetic anhydride 109-01-3, N-Methylpiperazine 124-40-3, reactions 141-43-5, 2-Aminoethanol, reactions 156-87-6 616-30-8, 3-Amino-1,2-propanediol 628-87-5, Iminodiacetonitrile 685-87-0, Diethyl bromomalonate 699-98-9, 2,3-Pyridinedicarboxylic anhydride 765-30-0, Cyclopropanamine 2508-29-4, 5-Amino-1-pentanol 3858-80-8, 3,5-Dimethylbenzylamine 4637-24-5, DMF dimethyl acetal 6850-57-3, 2-Methoxybenzylamine 13325-10-5, 4-Amino-1-butanol 13937-08-1, Diethyl hydroxymalonate 14505-28-3 18638-99-8, 3,4,5-Trimethoxybenzylamine 24687-79-4 26543-05-5 34967-24-3, 3,5-Dimethoxybenzylamine 39989-43-0, 3,5-Dichlorobenzylamine 40172-02-9 40172-06-3 41236-20-8, 3-Bromopropylamine hydrochloride 44565-27-7, 4-Amino-2-methyl-1-butanol 64362-32-9, 3-Benzoyl-2-pyridinecarboxylic acid 74975-27-2 80657-57-4 85068-29-7, 3,5-Bis(trifluoromethyl)benzylamine 88586-62-3, (S)-3-Amino-2-methyl-1-propanol 91692-76-1 104154-93-0 110239-06-0, Diethyl 4-phenyl-2,3-pyridinedicarboxylate 122853-70-7 147078-78-2
183551-06-6 183551-17-9 183551-51-1 183551-52-2 183551-53-3
183551-54-4 183551-60-2 183551-63-5 183551-65-7 **183551-67-9**
**183551-68-0** 183551-69-1 183551-70-4 183551-71-5
183812-31-9 205176-41-6 244107-37-7 244107-38-8 244107-39-9
244107-40-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of diazocinonaphthyridines, diazepinonaphthyridines, and related compds. having tachykinin receptor antagonistic activity)

IT 110171-23-8P 116060-91-4P 147078-85-1P 156241-24-6P 183550-72-3P
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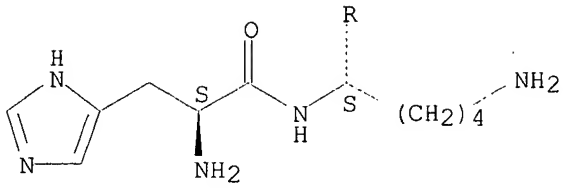
244107-41-3P 244107-43-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of diazocinonaphthyridines, diazepinonaphthyridines, and related compds. having tachykinin receptor antagonistic activity)

IT **86933-74-6**, Neurokinin A
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(antagonists; prepn. of diazocinonaphthyridines, diazepinonaphthyridines, and related compds. having tachykinin receptor antagonistic activity)

RN 86933-74-6 HCAPLUS
CN Neurokinin A (swine spinal cord) (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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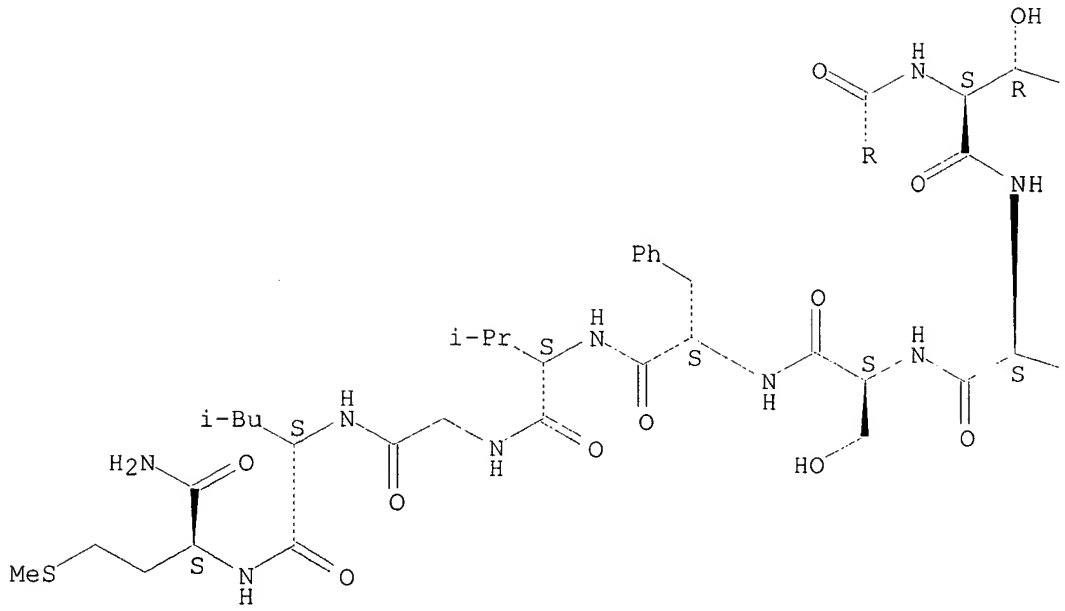

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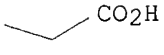

L118 ANSWER 8 OF 12 HCAPLUS COPYRIGHT 2003 ACS
AN 1998:427772 HCAPLUS
DN 129:95515

TI Preparation of medium-ring polycyclic heterocycles as tachykinin receptor antagonists
IN Natsugari, Hideaki; Ishimaru, Takenori; Doi, Takayuki; Ikeura, Yoshinori; Kimura, Chiharu; Tarui, Naoki
PA Takeda Chemical Industries, Ltd., Japan
SO U.S., 66 pp., Cont.-in-part of U.S. Ser. No. 621,360.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K031-33
ICS A61K031-55; C07D245-00; C07D487-00
NCL 514183000
CC 28-22 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 3

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| PI | US 5770590 | A | 19980623 | | US 1996-717801 | 19960923 | <-- |
| | JP 09263585 | A2 | 19971007 | | JP 1996-66337 | 19960322 | <-- |
| | JP 2976097 | B2 | 19991110 | | | | |
| | JP 09263587 | A2 | 19971007 | | JP 1997-20386 | 19960322 | <-- |
| | CN 1140172 | A | 19970115 | | CN 1996-106081 | 19960323 | <-- |
| | US 5786352 | A | 19980728 | | US 1996-621360 | 19960325 | <-- |
| | SG 69968 | A1 | 20000125 | | SG 1996-6546 | 19960325 | <-- |
| | US 6147071 | A | 20001114 | | US 1998-87894 | 19980601 | <-- |
| | US 6489315 | B1 | 20021203 | | US 2000-644306 | 20000823 | <-- |
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| | JP 1995-207553 | A | 19950720 | <-- | | | |
| | JP 1995-264727 | A | 19950918 | <-- | | | |
| | JP 1996-30033 | A | 19960123 | <-- | | | |
| | JP 1996-66337 | A | 19960322 | <-- | | | |
| | US 1996-621360 | A2 | 19960325 | <-- | | | |
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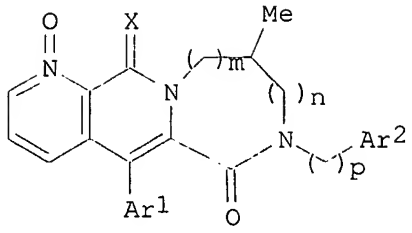
| | US 1998-87894 | A3 | 19980601 | <-- | | | |

OS MARPAT 129:95515
GI



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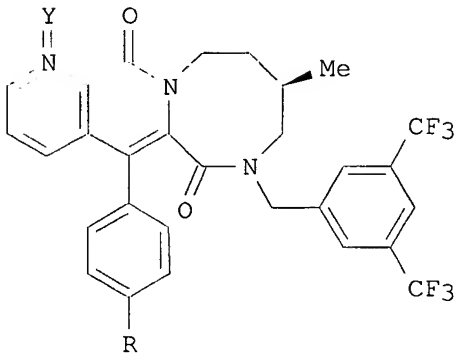

II

AB A variety of polycyclic heterocycles are disclosed, and in particular the compds. I and salts are claimed [wherein X = O, S; Ar1, Ar2 = certain (un)substituted Ph; m, n = 0 to 4; (m+n) = 2 to 4; p = 1 to 6]. The compds. show an excellent tachykinin receptor antagonistic effect. For instance, (9R)-7-[3,5-bis(trifluoromethyl)benzyl]-6,7,8,9,10,11-hexahydro-9-methyl-5-(4-methylphenyl)-6,13-dioxo-13H-[1,4]diazocino[2,1-g][1,7]naphthyridine, i.e., II [Y = absent, R = Me] (prepn. given) underwent hydroxylation by Streptomyces subrutilus IFO 13388 to give II [Y = absent, R = CH2OH] (III). The latter underwent acetylation with Ac2O and pyridine, N-oxidn. with m-ClC6H4C(O)OOH, and hydrolytic deacetylation, to give title compd. II [Y = O, R = CH2OH]. III had an ID50 of 2.5 .mu.g/kg i.v. for inhibiting capsaicin-induced tracheal plasma extravasation in anesthetized guinea pigs. I also showed substance P receptor antagonistic and NK2 receptor inhibitory activities.

ST heterocyclic prepn tachykinin receptor antagonist; diazocinonaphthyridine prepn substance P receptor antagonist

IT **Tachykinin receptors**
(**NK1 antagonists**; prepn. of medium-ring polycyclic heterocycles as tachykinin receptor antagonists)

IT **Tachykinin receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**NK1**, treatment of mediated diseases; prepn. of medium-ring polycyclic heterocycles as tachykinin receptor antagonists)

IT **Tachykinin receptors**
(**NK2 antagonists**; prepn. of medium-ring polycyclic heterocycles as tachykinin receptor antagonists)

IT **Tachykinin receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**NK2**, treatment of mediated diseases; prepn. of medium-ring polycyclic heterocycles as tachykinin receptor antagonists)

IT **Tachykinin receptors**
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(treatment of mediated diseases; prepn. of medium-ring polycyclic

heterocycles as tachykinin receptor antagonists)

IT 207606-22-2P 207606-26-6P
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of medium-ring polycyclic heterocycles as tachykinin receptor antagonists)

IT 183145-60-0P 183549-77-1P 183549-78-2P 183549-79-3P 183549-80-6P
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183549-86-2P 183549-87-3P 183549-88-4P 183549-89-5P 183549-90-8P
183549-91-9P 183549-92-0P 183549-93-1P 183549-94-2P 183549-95-3P
183549-96-4P 183549-97-5P 183549-98-6P 183550-00-7P 183550-02-9P
183550-03-0P 183550-05-2P 183550-07-4P 183550-08-5P 183550-09-6P
183550-10-9P 183550-11-0P 183550-13-2P 183550-15-4P 183550-16-5P
183550-18-7P 183550-20-1P 183550-21-2P 183550-23-4P 183550-26-7P
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183550-64-3P 183550-65-4P 183550-66-5P 183550-67-6P 183550-68-7P
183550-69-8P 183550-70-1P 207606-24-4P 207606-31-3P 207606-34-6P
209672-70-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of medium-ring polycyclic heterocycles as tachykinin receptor antagonists)

IT 67-63-0, Isopropanol, reactions 100-46-9, Benzylamine, reactions
102-49-8, 3,4-Dichlorobenzylamine 104-63-2, N-(2-Hydroxyethyl)benzenemethanamine 106-38-7, 4-Bromotoluene 109-01-3, 1-Methylpiperazine 109-73-9, n-Butylamine, reactions 110-89-4, Piperidine, reactions 110-91-8, Morpholine, reactions 156-87-6, 3-Amino-1-propanol 616-30-8, 3-Amino-1,2-propanediol 628-87-5, Iminodiacetonitrile 685-87-0, Diethyl bromomalonate 699-98-9, Pyridine-2,3-dicarboxylic acid anhydride 765-30-0, Cyclopropylamine 2508-29-4, 5-Amino-1-pentanol 5003-71-4 6850-57-3, 2-Methoxybenzylamine 13325-10-5, 4-Amino-1-butanol 13937-08-1, Diethyl hydroxymalonate 14505-28-3 18638-99-8, 3,4,5-Trimethoxybenzylamine 24687-79-4 32247-96-4, 3,5-Bis(trifluoromethyl)benzyl bromide 34967-24-3, 3,5-Dimethoxybenzylamine 40172-02-9 40172-06-3 44565-27-7, 4-Amino-2-methyl-1-butanol 64362-32-9, 3-Benzoyl-2-pyridinecarboxylic acid 74975-27-2, 4-(4-Methylbenzoyl)-3-pyridinecarboxylic acid 80657-57-4 85068-29-7, 3,5-Bis(trifluoromethyl)benzylamine 88586-62-3, (S)-3-Amino-2-methyl-1-propanol 104154-93-0 110239-06-0, Diethyl 4-phenyl-2,3-pyridinedicarboxylate 147078-78-2, 2-Chloro-4-phenyl-3-pyridinecarboxylic acid 183551-51-1, 3,5-Bis(trifluoromethyl)benzyl methanesulfonate 183551-52-2 183551-53-3 183551-54-4 183551-55-5 183551-69-1 183551-70-4 183551-71-5 183812-31-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of medium-ring polycyclic heterocycles as tachykinin receptor antagonists)

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183551-72-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of medium-ring polycyclic heterocycles as tachykinin receptor antagonists)

IT 33507-63-0, Substance P
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(treatment of mediated diseases; prepn. of medium-ring polycyclic heterocycles as tachykinin receptor antagonists)

RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD

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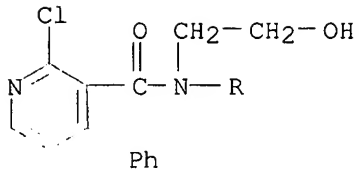
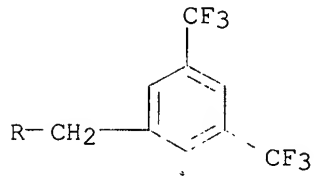
IT **183550-95-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of medium-ring polycyclic heterocycles as tachykinin receptor antagonists)

RN 183550-95-0 HCAPLUS
CN 3-Pyridinecarboxamide, N-[[3,5-bis(trifluoromethyl)phenyl]methyl]-2-chloro-N-(2-hydroxyethyl)-4-phenyl- (9CI) (CA INDEX NAME)





L118 ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2003 ACS
AN 1997:706935 HCAPLUS
DN 128:3591
TI Potent NK1 receptor antagonists: synthesis and antagonistic activity of various heterocycles with an N-[3,5-bis(trifluoromethyl)benzyl]-N-methylcarbamoyl substituent
AU Ikeura, Yoshinori; Tanaka, Toshimasa; Kiyota, Yutaka; Morimoto, Shinji; Ogino, Masaki; Ishimaru, Takenori; Kamo, Izumi; Doi, Takayuki; Natsugari, Hideaki
CS Pharmaceutical Research Division, Takeda Chemical Industries, Ltd., Osaka, 532, Japan
SO Chemical & Pharmaceutical Bulletin (**1997**), 45(10), 1642-1652
CODEN: CPBTAL; ISSN: 0009-2363
PB Pharmaceutical Society of Japan
DT Journal
LA English
CC 27-16 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1
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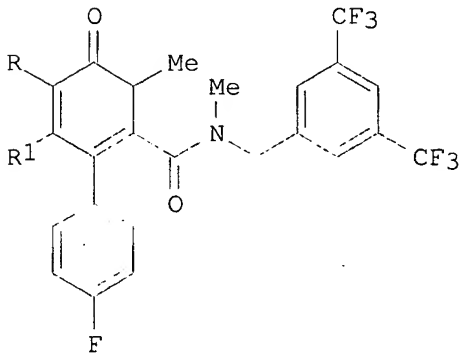

I

AB Various N-[3,5-bis(trifluoromethyl)benzyl]-N-methylcarbamoyl heterocycles modified at rings A and B in the isoquinolone and pyrido[3,4-b]pyridine nuclei were prepd. and evaluated for NK1 receptor antagonistic activities. The structure-activity relationship studies on this series, along with conformational anal., showed that for ring A, 6-membered heterocycles are preferable to 5-membered heterocycles (a ca. 300-fold difference in potency), the 6-membered ring seems to function as an anchor by fixing the

pendant Ph group in a desirable orientation for receptor binding, and since compds. with arom. rings and those with aliph. rings as ring B both show good potency, this ring does not seem to be essential for receptor recognition. Among the compds. synthesized, the tetrahydropyridine derivs. I [RR1 = NMe(CH2)3, CH2NMeCH2CH2, (CH2)3NMe] exhibited excellent inhibitory effects both in vitro and in vivo, with potent activity upon oral administration (ED50-0.20-0.27 mg/kg) (capsaicin-induced plasma extravasation in guinea pig trachea).

ST trifluoromethylbenzylcarbamoylnaphthyridine prepn NK1 receptor antagonist; naphthyridine trifluoromethylbenzylcarbamoyl prepn NK1 receptor antagonist

IT **Tachykinin receptors**
(**NK1 antagonists**; prepn. of N-[3,5-bis(trifluoromethyl)benzyl]-N-methylcarbamoylpyridinone analogs as potent **NK1** receptor antagonists)

IT 159817-70-6
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(prepn. of N-[3,5-bis(trifluoromethyl)benzyl]-N-methylcarbamoylpyridinone analogs as potent NK1 receptor antagonists)

IT 168541-21-7P 168541-28-4P 168541-66-0P 168541-83-1P 168541-85-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of N-[3,5-bis(trifluoromethyl)benzyl]-N-methylcarbamoylpyridinone analogs as potent NK1 receptor antagonists)

IT 159818-48-1P 168541-26-2P 168541-29-5P 168541-33-1P 168541-38-6P
168541-45-5P 168541-46-6P 168541-82-0P 198878-46-5P
**198878-48-7P** 198878-50-1P 198878-53-4P 198878-55-6P
198878-56-7P 198878-57-8P 198878-76-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of N-[3,5-bis(trifluoromethyl)benzyl]-N-methylcarbamoylpyridinone analogs as potent NK1 receptor antagonists)

IT 699-98-9, 2,3-Pyridinedicarboxylic anhydride 4664-08-8, 3,4-Pyridinedicarboxylic anhydride 6007-83-6, 2,3-Thiophenedicarboxylic anhydride 6007-85-8, 3,4-Thiophenedicarboxylic anhydride 17684-12-7 25808-30-4, N-Methylaminoacetonitrile hydrochloride 52605-49-9, Sarcosine ethyl ester hydrochloride 85068-29-7 85679-03-4 125064-63-3 159820-24-3 168543-12-2, 1-Methyl-2,3-pyrroledicarboxylic anhydride 198878-62-5 198878-64-7 198878-67-0 198878-68-1 198878-70-5 198878-82-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of N-[3,5-bis(trifluoromethyl)benzyl]-N-methylcarbamoylpyridinone analogs as potent NK1 receptor antagonists)

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168542-40-3P 168542-44-7P 168542-45-8P 168542-46-9P 168542-51-6P
168542-52-7P 168542-53-8P 168542-54-9P 168543-10-0P 198878-60-3P
198878-71-6P 198878-72-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of N-[3,5-bis(trifluoromethyl)benzyl]-N-methylcarbamoylpyridinone analogs as potent NK1 receptor antagonists)

RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD

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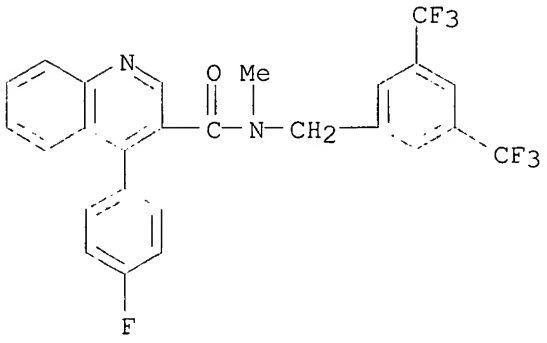
(33) Vassout, A; Neuropeptides 1994, V26(Suppl 1), P38
(34) Walsh, D; J Med Chem 1984, V27, P1317 HCAPLUS

IT **198878-48-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of N-[3,5-bis(trifluoromethyl)benzyl]-N-methylcarbamoylpyridinone analogs as potent NK1 receptor antagonists)

RN 198878-48-7 HCAPLUS

CN 3-Quinolinecarboxamide, N-[[3,5-bis(trifluoromethyl)phenyl]methyl]-4-(4-fluorophenyl)-N-methyl- (9CI) (CA INDEX NAME)




L118 ANSWER 10 OF 12 HCAPLUS COPYRIGHT 2003 ACS

AN 1996:728630 HCAPLUS

DN 126:8145

TI Preparation of polycyclic heterocycles as tachykinin receptor antagonists

IN Natsugari, Hideaki; Ishimaru, Takenori; Doi, Takayuki; Ikeura, Yoshinori; Kimura, Chiharu

PA Takeda Chemical Industries, Ltd., Japan

SO Eur. Pat. Appl., 94 pp.
CODEN: EPXXDW
DT Patent
LA English
IC ICM C07D471-14
ICS A61K031-495; C07D498-04; C07D471-04; C07D487-04
CC 28-22 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 3

| | PATENT NO. | KIND | DATE | | APPLICATION NO. | DATE | |
|---|---|---|---|---|---|---|---|
| PI | EP 733632 | A1 | 19960925 | | EP 1996-104500 | 19960321 | <-- |
| | R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE | | | | | | |
| | NO 9601160 | A | 19960925 | | NO 1996-1160 | 19960321 | <-- |
| | TW 394773 | B | 20000621 | | TW 1996-85103427 | 19960321 | <-- |
| | CA 2172421 | AA | 19960925 | | CA 1996-2172421 | 19960322 | <-- |
| | AU 9648261 | A1 | 19961003 | | AU 1996-48261 | 19960322 | <-- |
| | AU 699611 | B2 | 19981210 | | | | |
| | CN 1140172 | A | 19970115 | | CN 1996-106081 | 19960323 | <-- |
| | IL 117631 | A1 | 20001121 | | IL 1996-117631 | 19960324 | <-- |
| | BR 9601125 | A | 19980106 | | BR 1996-1125 | 19960325 | <-- |
| | SG 69968 | A1 | 20000125 | | SG 1996-6546 | 19960325 | <-- |
| | US 6489315 | B1 | 20021203 | | US 2000-644306 | 20000823 | <-- |
| PRAI | JP 1995-91436 | A | 19950324 | <-- | | | |
| | JP 1995-207553 | A | 19950720 | <-- | | | |
| | JP 1995-264727 | A | 19950918 | <-- | | | |
| | JP 1996-30033 | A | 19960123 | <-- | | | |
| | US 1996-621360 | A3 | 19960325 | <-- | | | |
| | US 1998-87894 | A3 | 19980601 | <-- | | | |

OS MARPAT 126:8145
GI For diagram(s), see printed CA Issue.
AB Title compds. [I; R = (CH2)nR4; R1,R2 = H or a substituent; R1R2 = atoms to complete a (hetero)cyclic ring; ring B = heterocyclic ring; R3,R4 = (hetero)cyclic ring; X-Y = N:C, C(O)N, C(S)N; n = 1-6] were prepd. Thus, 4-BrC6H4Me was condensed with 2,3-pyridinedicarboxylic acid and the product amidated by HN(CH2CN)2 to give, after cyclization in 5 addnl. steps, 7-[3,5-bis(trifluoromethyl)benzyl]-6,7,8,9-tetrahydro-5-(4-methylphenyl)-6,11-dioxo-11H-pyrazino[2,1-g][1,7]naphthyridine. Data for in vitro biol. activity of selected I were given.
ST heterocyclic prepn tachykinin receptor antagonist
IT **Tachykinin receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**NK2**, mediated diseases; treatment; prepn. of polycyclic heterocycles as tachykinin receptor antagonists)
IT **Tachykinin receptors**
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(mediated diseases; treatment; prepn. of polycyclic heterocycles as tachykinin receptor antagonists)
IT 33507-63-0, Substance P
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(mediated diseases; treatment; prepn. of polycyclic heterocycles as tachykinin receptor antagonists)
IT 183145-60-0P 183549-77-1P 183549-78-2P 183549-79-3P 183549-80-6P
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183549-86-2P 183549-87-3P 183549-88-4P 183549-89-5P 183549-90-8P
183549-91-9P 183549-92-0P 183549-93-1P 183549-94-2P 183549-95-3P
183549-96-4P 183549-97-5P 183549-98-6P 183550-00-7P 183550-02-9P
183550-03-0P 183550-05-2P 183550-07-4P 183550-08-5P 183550-09-6P
183550-10-9P 183550-11-0P 183550-13-2P 183550-15-4P 183550-16-5P
183550-18-7P 183550-20-1P 183550-21-2P 183550-23-4P 183550-26-7P

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183550-34-7P 183550-35-8P 183550-36-9P 183550-37-0P 183550-38-1P
183550-39-2P 183550-40-5P 183550-41-6P 183550-42-7P 183550-43-8P
183550-44-9P 183550-45-0P 183550-46-1P 183550-47-2P 183550-48-3P
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183550-54-1P 183550-55-2P 183550-56-3P 183550-57-4P 183550-58-5P
183550-59-6P 183550-60-9P 183550-61-0P 183550-62-1P 183550-63-2P
183550-64-3P 183550-65-4P 183550-66-5P 183550-67-6P 183550-68-7P
183550-69-8P 183550-70-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of polycyclic heterocycles as tachykinin receptor antagonists)

IT 67-63-0, Isopropanol, reactions 100-46-9, Benzylamine, reactions 102-49-8, 3,4-DichloroBenzylamine 104-63-2, N-(2-Hydroxyethyl)benzenemethanamine 106-38-7, 4-Bromotoluene 109-01-3, 1-Methylpiperazine 109-73-9, n-Butylamine, reactions 110-89-4, Piperidine, reactions 110-91-8, Morpholine, reactions 156-87-6, 3-Amino-1-propanol 616-30-8, 3-Amino-1,2-propanediol 628-87-5, Iminodiacetonitrile 685-87-0, Diethyl bromomalonate 699-98-9, Pyridine-2,3-dicarboxylic acid anhydride 765-30-0, Cyclopropylamine 2508-29-4, 5-Amino-1-pentanol 5003-71-4 6850-57-3, 2-Methoxybenzylamine 13325-10-5, 4-Amino-1-butanol 13937-08-1, Diethyl hydroxymalonate 14505-28-3 18638-99-8, 3,4,5-Trimethoxybenzylamine 24687-79-4 32247-96-4, 3,5-Bis(trifluoromethyl)benzyl bromide 34967-24-3, 3,5-Dimethoxybenzylamine 40172-02-9 40172-06-3 44565-27-7, 4-Amino-2-methyl-1-butanol 64362-32-9, 3-Benzoyl-2-pyridinecarboxylic acid 74975-27-2, 4-(4-Methylbenzoyl)-3-pyridinecarboxylic acid 85068-29-7, 3,5-Bis(trifluoromethyl)benzylamine 88586-62-3, (S)-3-Amino-2-methyl-1-propanol 104154-93-0 110239-06-0, Diethyl 4-phenyl-2,3-pyridinedicarboxylate 147078-78-2, 2-Chloro-4-phenyl-3-pyridinecarboxylic acid 183551-51-1, 3,5-Bis(trifluoromethyl)benzyl methanesulfonate 183551-52-2 183551-53-3 183551-54-4 183551-55-5 183551-69-1 183551-70-4 183551-71-5 183812-31-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of polycyclic heterocycles as tachykinin receptor antagonists)

IT 116060-91-4P 147078-85-1P 156241-24-6P 183550-71-2P 183550-72-3P
183550-73-4P 183550-74-5P 183550-75-6P 183550-76-7P 183550-77-8P
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183550-83-6P 183550-84-7P 183550-85-8P 183550-86-9P 183550-87-0P
183550-88-1P 183550-89-2P 183550-90-5P 183550-91-6P 183550-92-7P
183550-93-8P 183550-94-9P **183550-95-0P** 183550-96-1P
183550-97-2P 183550-98-3P 183550-99-4P 183551-00-0P 183551-01-1P
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183551-06-6P 183551-07-7P **183551-08-8P 183551-09-9P**
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183551-14-6P 183551-15-7P **183551-16-8P** 183551-17-9P
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183551-43-1P 183551-44-2P 183551-45-3P 183551-46-4P
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**183551-61-3P** 183551-62-4P 183551-63-5P 183551-64-6P
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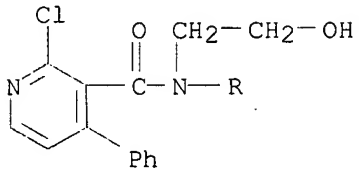
183551-72-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

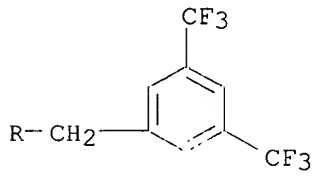
(Reactant or reagent)
(prepn. of polycyclic heterocycles as tachykinin receptor antagonists)

IT **183550-95-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of polycyclic heterocycles as tachykinin receptor antagonists)

RN 183550-95-0 HCAPLUS

CN 3-Pyridinecarboxamide, N-[[3,5-bis(trifluoromethyl)phenyl]methyl]-2-chloro-N-(2-hydroxyethyl)-4-phenyl- (9CI) (CA INDEX NAME)




L118 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2003 ACS

AN 1995:835514 HCAPLUS

DN 123:256684

TI Preparation of pyridopyridinecarboxamides, thienopyridinecarboxamides, and related compounds as tachykinin antagonists and inhibitors of plasma extravasation.

IN Natsugari, Hideaki; Ishimaru, Takenori; Doi, Takayuki

PA Takeda Chemical Industries, Ltd., Japan

SO Eur. Pat. Appl., 72 pp.
CODEN: EPXXDW

DT Patent

LA English

IC ICM C07D471-04
ICS C07D495-04; C07D513-04; C07D401-04; C07D409-04; A61K031-33; A61K031-47

CC 28-2 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63

FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI EP 652218 | A1 | 19950510 | EP 1994-117576 | 19941108 <-- |
| EP 652218 | B1 | 20010711 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE | | | | |
| NO 9404252 | A | 19950511 | NO 1994-4252 | 19941108 <-- |
| AT 203024 | E | 20010715 | AT 1994-117576 | 19941108 <-- |
| CA 2135440 | AA | 19950511 | CA 1994-2135440 | 19941109 <-- |
| FI 9405281 | A | 19950511 | FI 1994-5281 | 19941109 <-- |
| AU 9477738 | A1 | 19950518 | AU 1994-77738 | 19941109 <-- |
| AU 678295 | B2 | 19970522 | | |
| BR 9404403 | A | 19950718 | BR 1994-4403 | 19941109 <-- |
| JP 08067678 | A2 | 19960312 | JP 1994-274699 | 19941109 <-- |
| RU 2135471 | C1 | 19990827 | RU 1994-40174 | 19941109 <-- |
| HU 68810 | A2 | 19950519 | HU 1994-3230 | 19941110 <-- |
| CN 1107476 | A | 19950830 | CN 1994-113866 | 19941110 <-- |

| | | | | | | |
|---|---|---|---|---|---|---|
| | CN 1052004 | B | 20000503 | | | |
| | US 5585385 | A | 19961217 | US 1994-338762 | 19941110 <-- | |
| | BR 9501976 | A | 19960430 | BR 1995-1976 | 19950509 <-- | |
| PRAI | JP 1993-281178 | A | 19931110 <-- | | | |
| | JP 1993-337488 | A | 19931228 <-- | | | |
| | JP 1994-33637 | A | 19940303 <-- | | | |
| | JP 1994-138551 | A | 19940621 <-- | | | |

OS MARPAT 123:256684

GI For diagram(s), see printed CA Issue.

AB Title compds. [I; ring A, ring B = (substituted) homo- or heterocyclyl, .gtoreq.1 of them = (substituted) heterocyclyl; ring C = (substituted) benzene ring; R = H, (substituted) hydrocarbyl; 1 of X, Y = NR1, O; the other = CO, CS; or 1 of them = N: and the other = :CR2; R1 = H, (substituted) hydrocarbyl; R2 = H, halo, (substituted) hydrocarbyl, amino, OH; n = 1, 2], were prepd. Thus, 5-(4-fluorophenyl)-7,8-dihydro-7-methyl-8-oxo-6-pyrido[3,4-b]pyridinecarboxylic acid (prepn. given) was refluxed with SOCl2 in benzene and ther residue in THF was refluxed with N-[3,5-bis(trifluoromethyl)benzyl]methylamine and Et3N to give N-[3,5-bis(trifluoromethyl)benzyl]-5-(4-fluorophenyl)-7,8-dihydro-N,7-dimethyl-8-oxo-6-pyrido[3,4-b]pyridinecarboxamide (II). II inhibited substance P binding to IM-9 human lymphoblasts with IC50 = 0.08 nM. Tablets contg. II were prepd.

ST pyridopyridinecarboxamide prepn tachykinin antagonist; plasma extravasation inhibitor pyridopyridinecarboxamide; thienopyridinecarboxamide prepn plasma extravasation inhibitor

IT Plasma
(extravasation; prepn. of pyridopyridinecarboxamides, thienopyridinecarboxamides, and related compds. as tachykinin antagonists and inhibitors of plasma extravasation)

IT Urinary tract
(treatment of disorders of micturition; prepn. of pyridopyridinecarboxamides, thienopyridinecarboxamides, and related compds. as tachykinin antagonists and inhibitors of plasma extravasation)

IT **Kinins (animal hormones)**
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(**tachykinins**, antagonists; prepn. of pyridopyridinecarboxamides, thienopyridinecarboxamides, and related compds. as tachykinin antagonists and inhibitors of plasma extravasation)

IT 168541-32-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(4prepn. of pyridopyridinecarboxamides, thienopyridinecarboxamides, and related compds. as tachykinin antagonists and inhibitors of plasma extravasation)

IT 33507-63-0, Substance P
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(antagonists; prepn. of pyridopyridinecarboxamides, thienopyridinecarboxamides, and related compds. as tachykinin antagonists and inhibitors of plasma extravasation)

IT 168541-17-1P 168541-18-2P 168541-19-3P 168541-20-6P 168541-21-7P
168541-22-8P 168541-23-9P **168541-24-0P** 168541-25-1P
168541-26-2P 168541-27-3P 168541-28-4P 168541-29-5P 168541-30-8P
168541-31-9P 168541-33-1P 168541-34-2P 168541-35-3P 168541-36-4P
168541-37-5P 168541-38-6P 168541-39-7P 168541-40-0P 168541-41-1P
168541-42-2P 168541-43-3P 168541-44-4P 168541-45-5P 168541-46-6P
168541-47-7P 168541-48-8P 168541-49-9P 168541-50-2P 168541-51-3P
168541-52-4P 168541-53-5P 168541-54-6P 168541-55-7P 168541-56-8P
168541-57-9P 168541-58-0P 168541-59-1P 168541-60-4P 168541-61-5P

168541-62-6P 168541-63-7P 168541-64-8P 168541-65-9P 168541-66-0P
168541-67-1P 168541-68-2P 168541-69-3P 168541-70-6P 168541-71-7P
168541-72-8P 168541-73-9P 168541-74-0P 168541-75-1P 168541-76-2P
168541-77-3P 168541-78-4P 168541-79-5P 168541-80-8P 168541-81-9P
168541-82-0P 168541-83-1P 168541-84-2P 168541-85-3P 168541-86-4P
168541-87-5P 168541-88-6P 168541-89-7P 168541-90-0P 168541-91-1P
168541-92-2P 168543-19-9P 168543-20-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of pyridopyridinecarboxamides, thienopyridinecarboxamides, and related compds. as tachykinin antagonists and inhibitors of plasma extravasation)

IT 71-43-2, Benzene, reactions 74-88-4, Methyl iodide, reactions 74-89-5, Methylamine, reactions 85-44-9, 1,3-Isobenzofurandione 87-13-8, Diethyl ethoxymethylenemalonate 95-46-5, 2-Bromotoluene 100-58-3, Phenylmagnesium bromide 105-53-3 106-38-7, 4-Bromotoluene 108-86-1, BromoBenzene, reactions 110-02-1, Thiophene 122-07-6, Methylaminoacetaldehyde dimethyl acetal 460-00-4, 1-Bromo-4-fluorobenzene 462-06-6, Fluorobenzene 699-98-9, 2,3-Pyridinedicarboxylic anhydride 931-50-0, Cyclohexylmagnesium bromide 932-31-0, 2-Methylphenylmagnesium bromide 4640-67-9, 4-Fluorobenzoylacetonitrile 4664-08-8, 3,4-Pyridinedicarboxylic anhydride 4744-50-7, 2,3-Pyrazinedicarboxylic anhydride 5664-52-8, 4,5-Thiazoledicarboxylic anhydride 6007-83-6, 2,3-Thiophenedicarboxylic anhydride 6007-85-8, 3,4-Thiophenedicarboxylic anhydride 13139-86-1, 4-Methoxylphenylmagnesium bromide 25808-30-4, N-Methylaminoacetonitrile hydrochloride 28987-79-3, 3-Methylphenylmagnesium bromide 32247-96-4, 3,5-Bistrifluoromethyl benzyl bromide 40018-26-6, 2,5-Dihydroxy-1,4-dithiane 42471-56-7, 2-(2-Aminobenzoyl)pyridine 52605-49-9, N-Methylglycine ethyl ester hydrochloride 116060-91-4 159820-24-3 168543-12-2, 1-Methylpyrrole-2,3-dicarboxylic anhydride
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of pyridopyridinecarboxamides, thienopyridinecarboxamides, and related compds. as tachykinin antagonists and inhibitors of plasma extravasation)

IT 30006-03-2P 40298-32-6P 46496-80-4P 74975-25-0P 74975-27-2P
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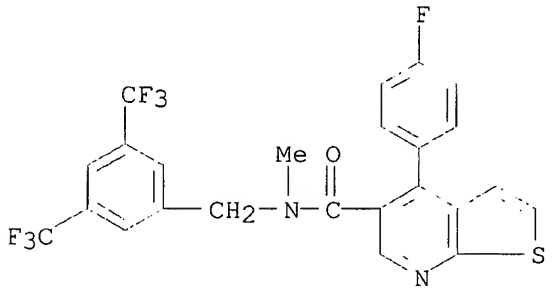
168543-14-4P 168543-15-5P 168543-16-6P 168543-17-7P 168543-18-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of pyridopyridinecarboxamides, thienopyridinecarboxamides, and related compds. as tachykinin antagonists and inhibitors of plasma extravasation)

IT **168541-24-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of pyridopyridinecarboxamides, thienopyridinecarboxamides, and related compds. as tachykinin antagonists and inhibitors of plasma extravasation)

RN 168541-24-0 HCAPLUS
CN Thieno[2,3-b]pyridine-5-carboxamide, N-[[3,5-bis(trifluoromethyl)phenyl]methyl]-4-(4-fluorophenyl)-N-methyl- (9CI) (CA INDEX NAME)




L118 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2003 ACS
AN 1995:257714 HCAPLUS
DN 122:56051
TI Condensed heterocyclic compounds, their production and use
IN Natsugari, Hideaki; Ikeda, Hitoshi; Ishimaru, Takenori; Doi, Takayuki
PA Takeda Chemical Industries, Ltd., Japan
SO Eur. Pat. Appl., 161 pp.
CODEN: EPXXDW
DT Patent
LA English
IC ICM C07D217-24
ICS C07D217-26; C07D311-18; C07D215-54; C07D471-04; C07D311-76; C07D215-22; A61K031-47; A61K031-37
CC 28-17 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 1

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| PI | EP 585913 | A2 | 19940309 | EP 1993-114024 | 19930902 <-- |
| | EP 585913 | A3 | 19940525 | | |
| | EP 585913 | B1 | 19971229 | | |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE | | | | |
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| | NO 179904 | B | 19960930 | | |
| | NO 179904 | C | 19970108 | | |
| | US 5482967 | A | 19960109 | US 1993-114841 | 19930902 <-- |
| | AT 161530 | E | 19980115 | AT 1993-114024 | 19930902 <-- |
| | CA 2105518 | AA | 19940305 | CA 1993-2105518 | 19930903 <-- |
| | AU 9346132 | A1 | 19940310 | AU 1993-46132 | 19930903 <-- |
| | AU 667739 | B2 | 19960404 | | |
| | FI 9303857 | A | 19940517 | FI 1993-3857 | 19930903 <-- |
| | JP 07010844 | A2 | 19950113 | JP 1993-220333 | 19930903 <-- |

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| PRAI | JP 1992-237481 | | 19920904 | <-- | | |
| | JP 1993-103328 | | 19930428 | <-- | | |
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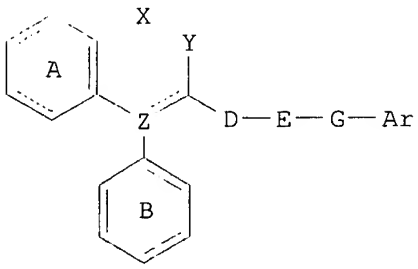
OS MARPAT 122:56051

GI


I


AB Novel compds. represented by I were prepd.; ring A may be substituted; ring B represents an optionally substituted benzene ring; either X or Y represents -NR1- (R1 represents a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted hydroxyl group or an optionally substituted amino group), -O- or -S-, the other representing -CO-, -CS-, or -C(R2)R2a- (R2 and R2a independently represent a hydrogen atom or an optionally substituted hydrocarbon group), or either X or Y represents -N=, the other representing =CR3- (R3 represents a hydrogen atom, a halogen atom, an optionally substituted hydrocarbon group, an optionally substituted amino group, a substituted hydroxyl group or a mercapto group substituted by an optionally substituted hydrocarbon group); ---- represents a single or double bond; when ---- is a single bond, Z represents -CR4- (R4 represents a hydrogen atom, hydroxyl group or an optionally substituted hydrocarbon group) or a nitrogen atom, or (ii) when ---- is a double bond, Z represents a carbon atom. D represents a C1-3 alkylene group which may be substituted by an oxo group or a thioxo group, or D and Y, taken together, may form a 5- to 7-membered ring which may be substituted by an oxo group or a thioxo group; E represents -NR5- (R5 represents a hydrogen atom or an optionally substituted hydrocarbon group), -O- or -S-(O)n- (n is 0, 1 or 2), or R5 and Y, taken together, may form a 5- to 7-membered ring which may be substituted by an oxo group or a thioxo group. G represents a bond or a C1-3 alkylene group. Ar represents an optionally substituted aryl or heterocyclic group. Some representative prepd. compds. were benzopyran-, quinoline-, isoquinoline- and quinoxalinecarboxamides. I and its salts have an excellent activity of inhibiting ACAT, lowering cholesterol in blood and inhibiting tachykinin receptor (test data given).


ST heterocyclic compd prepn biol activity; cholesterol acyl transferase inhibitor heterocyclic compd; blood cholesterol lowering heterocyclic compd; tachykinin receptor inhibiting heterocyclic compd; benzopyran compd prepn biol activity; isoquinoline compd prepn biol activity; quinoline compd prepn biol activity; quinoxaline compd prepn biol activity

IT Anticholesteremics and Hypolipemics
(condensed heterocyclic compds.)

IT **Kinin receptors**
**Receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**tachykinin**, inhibitors for, condensed heterocyclic compds.

as)
IT 9027-63-8, Cholesterol acyltransferase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(condensed heterocyclic compds. as inhibitors for)
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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and biol. activity of)
IT 159818-44-7P 159818-45-8P 159818-46-9P 159818-47-0P 159818-48-1P
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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and biol. activity of)

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159820-36-7P 159820-38-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reaction of, in prepn. of biol. active condensed heterocyclic compds.)

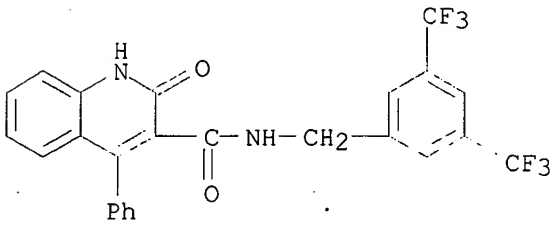
IT 50-00-0, Formaldehyde, reactions 75-30-9, Isopropyl iodide 79-04-9, Chloroacetyl chloride 100-39-0, Benzyl bromide 100-46-9, Benzylamine, reactions 105-53-3, Diethyl malonate 107-15-3, 1,2-Ethanediamine, reactions 108-00-9 124-63-0, Methanesulfonyl chloride 135-02-4, o-Anisaldehyde 367-25-9, 2,4-Difluoroaniline 447-61-0 623-12-1, 4-Chloroanisole 685-87-0, Diethyl bromomalonate 933-88-0, o-Toluoyl chloride 1470-57-1 2426-02-0 5266-85-3 5292-43-3, tert-Butyl bromoacetate 5779-95-3, 3,5-Dimethylbenzaldehyde 5959-36-4 6850-57-3, 2-Methoxybenzylamine 7035-02-1, 2-Methoxybenzyl chloride 7417-18-7 7649-92-5 18936-32-8 24544-04-5, 2,6-Diisopropylaniline 25808-30-4 26832-76-8 28773-68-4 32247-96-4 33184-58-6 37393-68-3 37617-98-4 52605-49-9 68817-71-0 78945-92-3 78945-97-8 81698-18-2 85068-29-7 92795-47-6 128831-20-9 128832-35-9 135030-74-9 136280-97-2 136281-10-2 137711-59-2 137711-72-9 137711-73-0 142256-41-5 142256-46-0 142256-53-9 152818-36-5 159820-23-2 159820-24-3 159820-27-6 159820-28-7 159820-29-8 159820-31-2 159820-32-3 159820-33-4 159820-37-8
RL: RCT (Reactant); RACT (Reactant or reagent)

(reaction of, in prepn. of biol. active condensed heterocyclic compds.)

IT **159818-59-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and biol. activity of)

RN 159818-59-4 HCAPLUS

CN 3-Quinolinecarboxamide, N-[[3,5-bis(trifluoromethyl)phenyl]methyl]-1,2-dihydro-2-oxo-4-phenyl- (9CI) (CA INDEX NAME)

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SET COST OFF

FILE 'REGISTRY' ENTERED AT 07:01:40 ON 04 MAR 2003

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| L1 | | STR |
| L2 | 19 | S L1 |
| L3 | 594 | S L1 FUL |
| | | SAV L3 KWON071/A |

FILE 'HCAPLUS' ENTERED AT 07:07:47 ON 04 MAR 2003

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| L4 | 40 | S L3 |
| | | E BUSER S/AU |
| L5 | 10 | S E3,E6,E7 |
| | | E FORD A/AU |
| L6 | 33 | S E3,E16,E17 |
| L7 | 37 | S E63,E65 |
| | | E FORD TONY/AU |
| | | E HOFFMANN T/AU |
| L8 | 135 | S E3-E9 |
| | | E HOFFMANN TOR/AU |
| L9 | 57 | S E4 |
| | | E LENZ B/AU |
| L10 | 29 | S E3-E9 |
| | | E SLEIGHT A/AU |
| L11 | 52 | S E4,E6-E8 |
| | | E VANKAN P/AU |
| L12 | 23 | S E3-E5 |
| | | E ROCHE/PA,CS |
| L13 | 21472 | S E3,E4 |
| L14 | 61 | S E27-E46 |
| | | E ROHAN/PA,CS |
| L15 | 2 | S E3,E4 |
| L16 | 10 | S L4 AND L5-L15 |
| | | E PROSTATE/CT |
| | | E E5+ALL |
| L17 | 2309 | S E2 |
| L18 | 1988 | S E12 |
| L19 | 22609 | S E20-E19+NT |

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L20           1 S L4 AND L17-L19
L21           1 S L4 AND (BPH OR BENIGN (L) PROSTAT? (L) (HYPERPLAS? OR HYPERTR
L22           1 S L20,L21
L23           1 S L22 AND L16
L24         969 S (NK OR NEUROKININ OR NEURO KININ)()1 (L) RECEPTOR (L) (ANTAGO
L25           5 S L24 AND L17-L19
L26           2 S L24 AND (BPH OR BENIGN (L) PROSTAT? (L) (HYPERPLAS? OR HYPERT
L27           6 S L25,L26
L28           1 S L23 AND L27
L29           5 S L27 NOT L28
                SEL DN AN 1 4 5
L30           3 S E1-E7 AND L29
L31           4 S L28,L30 AND (NK OR NK1 OR NEUROKININ OR TACHYKIN? OR RECEPTOR
L32           4 S L28,L30,L31
L33          39 S L4 AND (PD<=20010423 OR PRD<=20010423 OR AD<=20010423)
L34          47 S GR205171 OR GR()(205171 OR 205 171)
L35           5 S HSP117 OR HSP 117
L36          36 S L703606 OR L()(703606 OR 703 606)
L37          23 S L668169 OR L()(668169 OR 668 169)
L38           4 S LY303241 OR LY()(303241 OR 303 241)
L39          12 S LY306740 OR LY()(306740 OR 306 740)
L40          21 S MK869 OR MK 869
L41           6 S R544 OR R 544
L42           5 S SPANTIDE III
L43          11 S WIN62577 OR WIN()(62577 OR 62 577)
L44           5 S GR103537 OR GR()(103537 OR 103 537)
L45          13 S L758298 OR L()(758298 OR 758 298)
L46           9 S NKP608 OR NKP 608
L47          17 S CGP49823 OR CGP()(49823 OR 49 823)
L48         494 S CP96345 OR CP()(96345 OR 96 345)
L49         246 S CP99994 OR CP()(99994 OR 99 994)
L50          24 S CP122721 OR CP()(122721 OR 122 721)
L51         129 S FK888 OR FK 888
L52         119 S GR82334 OR GR()(82334 OR 82 334)
L53          41 S GR94800 OR GR()(94800 OR 94 800)
L54          20 S L733060 OR L()(733060 OR 733 060)
L55          16 S L742694 OR L()(742694 OR 742 694)
L56          10 S L754030 OR L()(754030 OR 754 030)
L57          30 S LY303870 OR LY()(303870 OR 303 870)
L58           9 S MEN11149 OR MEN()(11149 OR 11 149)
L59          10 S PD154075 OR PD()(154075 OR 154 075)
L60         250 S RP67580 OR RP()(67580 OR 67 580)
L61          18 S RPR100893 OR RPR()(100893 OR 100 893)
L62           1 S SPENDIDE
L63          32 S SENDIDE
L64          55 S SPANTIDE II
L65         217 S SR140333 OR SR()(140333 OR 140 333)
L66           0 S WIN41708 OR WIN()(41708 OR 41 708)
L67          11 S WIN62577 OR WIN()(62577 OR 62 577)
L68         410 S SR48968 OR SR()(48968 OR 48 968)
L69          69 S L659877 OR L()(659877 OR 659 877)
L70          74 S MEN10627 OR MEN()(10627 OR 10 627)
L71          14 S SR144190 OR SR()(144190 OR 144 190)
L72          41 S GR94800 OR GR()(94800 OR 94 800)
L73         149 S SR142801 OR SR()(142801 OR 142 801)
L74         159 S R820 OR R 820
L75          14 S R486 OR R 486
L76          13 S SB222200 OR SB()(222200 OR 222 200)
L77          13 S L758298 OR L()(758298 OR 758 298)
L78           0 S NK608 OR NK 608
L79           3 S MK608 OR MK 608
L80           2 S CGP47899 OR CGP()(47899 OR 47 899)
L81          16 S MEN11467 OR MEN()(11467 OR 11 467)
```

```
L82          18 S GR203040 OR GR()(203040 OR 203 040)
L83          13 S L732138 OR L()(732138 OR 732 138)
L84           1 S L4 AND L34-L83
L85           2 S WIN41908 OR WIN()(41908 OR 41 908)
L86         349 S SPANTIDE
L87           1 S L4 AND L85,L86
L88           1 S L84,L87
                SEL RN

     FILE 'REGISTRY' ENTERED AT 07:50:53 ON 04 MAR 2003
L89         186 S E8-E193
L90         129 S L89 AND L3
L91           1 S 351383-26-1
L92          56 S L89 NOT L90,L91
L93           7 S 123-90-0 OR 3282-30-2 OR 4548-45-2 OR 16419-60-6 OR 139911-29
L94           6 S 471938-15-5 OR 474026-15-8 OR 474026-16-9 OR 474026-17-0 OR 4
L95          43 S L92 NOT L93,L94
L96           6 S 144177-32-2 OR 351383-26-1 OR 170729-80-3 OR 145194-26-9 OR 1

     FILE 'REGISTRY' ENTERED AT 07:57:44 ON 04 MAR 2003
L97          46 S L95,L96

     FILE 'HCAPLUS' ENTERED AT 07:58:26 ON 04 MAR 2003
L98         964 S L97
L99           3 S L4 AND L98
L100          3 S L88,L99
L101          3 S L100 AND L4-L16
L102          6 S L32,L101
                E TACKYKININ RECEPTOR/CT
                E TACHYKININ RECEPTOR/CT
L103       1581 S E5,E6
L104        223 S E14
                E E4+ALL
L105       3707 S E10,E11,E9+NT
                E E27+ALL
L106       2037 S E8,E7+NT
                E E6+ALL
L107       3401 S E7,E8,E6+NT
                E E20
L108       2087 S E3-E21
L109        638 S E22-E25
L110         13 S L4 AND L103-L109
L111          3 S L102 AND L110
L112          6 S L102,L111
L113          6 S L112 AND L4-L88
L114          3 S L113 AND L17-L19
L115          2 S L113 AND (BHP OR BENIGN(L)PROSTAT?(L)HYPER?)
L116          4 S L114,L115
L117         12 S L110,L113 NOT L116
L118         12 S L117 AND L4-L88,L98-L109

     FILE 'REGISTRY' ENTERED AT 08:04:28 ON 04 MAR 2003

     FILE 'HCAPLUS' ENTERED AT 08:04:40 ON 04 MAR 2003

     FILE 'EMBASE' ENTERED AT 08:05:33 ON 04 MAR 2003
                E BENIGN PROSTAT/CT
                E E4+ALL
                E E2+ALL
L119       9419 S E1
L120       6565 S E7/BI OR E8/BI OR E11-E21/BI
L121       6986 S BHP OR BENIGN(L)PROSTAT?(L)HYPER?
L122          0 S L3
```

```
L123        1337 S L24
                 E NERUOKININE 1 RECEPTOR ANTAGONIST/CT
                 E NEUROKININE 1 RECEPTOR ANTAGONIST/CT
                 E NEUROKININ 1 RECEPTOR ANTAGONIST/CT
                 E E3+ALL
L124         663 S E1+NT
L125           1 S L119-L121 AND L123,L124

     FILE 'MEDLINE' ENTERED AT 08:08:33 ON 04 MAR 2003
L126           0 S L3
L127       13566 S L120 OR L121
                 E BENIGN PROSTAT/CT
                 E E5+ALL
                 E E2+ALL
L128       11113 S E5+NT
L129        1074 S E17/BI OR E23/BI
L130       13795 S L127-L129
L131        1451 S L24
                 E NEUROKININ 1 RECEPTOR/CT
                 E E4+ALL
                 E E2+ALL
L132        2169 S E15+NT
L133        2169 S E15/CN
L134        3283 S E14+NT
L135         680 S E14/CN
L136           0 S L130 AND L131-L135

=> fil embase
FILE 'EMBASE' ENTERED AT 08:10:58 ON 04 MAR 2003
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 FILE COVERS 1974 TO 27 Feb 2003 (20030227/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d all l125

L125 ANSWER 1 OF 1  EMBASE  COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN   97132738  EMBASE
DN   1997132738
TI   The 98th Annual Meeting of the American Society for Clinical Pharmacology
     and Therapeutics.
AU   Heydorn W.E.
CS   W.E. Heydorn, Pharmaceutical Operations, Synaptic Pharmaceutical
     Corporation, 215 College Road, Paramus, NJ 07652, United States.
     heydorn@aol.com
SO   Expert Opinion on Investigational Drugs, (1997) 6/4 (453-457).
     Refs: 10
     ISSN: 1354-3784  CODEN: EOIDER
CY   United Kingdom
DT   Journal; Conference Article
FS   008     Neurology and Neurosurgery
     015     Chest Diseases, Thoracic Surgery and Tuberculosis
     022     Human Genetics
     028     Urology and Nephrology
     049     Forensic Science Abstracts
     030     Pharmacology
     037     Drug Literature Index
     038     Adverse Reactions TitlesDrug Literature Index
LA   English
```

SL English

AB The 98th Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics was held on March 5-8, 1997. Over 850 researchers and clinicians pre-registered for this meeting. Papers presented at the conference focused on new observations. Firstly, novel therapeutic agents were discussed, then compounds that represent standard therapy for a number of different disease states were addressed. State of the art lectures provided concise updates on the status of a number of different issues. The following is a summary of some of the highlights and presentations at the conference. This summary is divided into four sections. Section 1 focuses on the Public Policy Debate on the ethics and utility of the placebo-controlled trial. Part 2 is a summary of the current status of gene therapy with particular reference to cystic fibrosis treatment. Part 3 is a summary of data on two recently approved compounds (donepezil and zafirlukast). The last part of this article discusses the results of drug therapy in two different disease states ( **benign prostatic hypertrophy** and migraine).

CT Medical Descriptors:
*cystic fibrosis
*gene therapy
*medical ethics
*migraine
***prostate hypertrophy**
alzheimer disease: DT, drug therapy
asthma: DT, drug therapy
clinical pharmacology
clinical trial
conference paper
drug approval
drug metabolism
human
hypotension: SI, side effect
medical research
vertigo: SI, side effect
Drug Descriptors:
cholinesterase inhibitor: PD, pharmacology
cholinesterase inhibitor: PK, pharmacokinetics
cholinesterase inhibitor: DT, drug therapy
cholinesterase inhibitor: CT, clinical trial
donepezil: PD, pharmacology
donepezil: PK, pharmacokinetics
donepezil: DT, drug therapy
donepezil: CT, clinical trial
doxazosin: PK, pharmacokinetics
doxazosin: CT, clinical trial
doxazosin: DT, drug therapy
eletriptan: DT, drug therapy
eletriptan: PD, pharmacology
eletriptan: CT, clinical trial
eletriptan: PK, pharmacokinetics
lanepitant: CT, clinical trial
lanepitant: DT, drug therapy
lanepitant: PD, pharmacology
leukotriene receptor blocking agent: PD, pharmacology
leukotriene receptor blocking agent: PK, pharmacokinetics
leukotriene receptor blocking agent: DT, drug therapy
leukotriene receptor blocking agent: IT, drug interaction
leukotriene receptor blocking agent: CT, clinical trial
ly 303780
**neurokinin 1 receptor antagonist: PD, pharmacology**
**neurokinin 1 receptor antagonist: DT, drug therapy**
**neurokinin 1 receptor antagonist: CT, clinical trial**
placebo

```
     serotonin 1d receptor agonist: CT, clinical trial
     serotonin 1d receptor agonist: DT, drug therapy
     serotonin 1d receptor agonist: PK, pharmacokinetics
     serotonin 1d receptor agonist: PD, pharmacology
     tacrine: DT, drug therapy
     terazosin: AE, adverse drug reaction
     terazosin: DT, drug therapy
     warfarin: IT, drug interaction
     warfarin: PK, pharmacokinetics
     zafirlukast: PD, pharmacology
     zafirlukast: PK, pharmacokinetics
     zafirlukast: IT, drug interaction
     zafirlukast: CT, clinical trial
     zafirlukast: DT, drug therapy
     unclassified drug
RN   (donepezil) 120011-70-3, 120014-06-4; (doxazosin) 74191-85-8; (eletriptan)
     143322-58-1; (lanepitant) 167678-33-3, 170508-05-1, 170566-84-4; (tacrine)
     1684-40-8, 3198-41-2, 321-64-2; (terazosin) 63074-08-8, 63590-64-7;
     (warfarin) 129-06-6, 2610-86-8, 3324-63-8, 5543-58-8, 81-81-2;
     (zafirlukast) 107753-78-6
CN   (1) Ly 303780
CO   (1) Lilly


=> d his

     (FILE 'HOME' ENTERED AT 07:01:07 ON 04 MAR 2003)
               SET COST OFF

     FILE 'REGISTRY' ENTERED AT 07:01:40 ON 04 MAR 2003
L1                STR
L2             19 S L1
L3            594 S L1 FUL
                  SAV L3 KWON071/A

     FILE 'HCAPLUS' ENTERED AT 07:07:47 ON 04 MAR 2003
L4             40 S L3
                  E BUSER S/AU
L5             10 S E3,E6,E7
                  E FORD A/AU
L6             33 S E3,E16,E17
L7             37 S E63,E65
                  E FORD TONY/AU
                  E HOFFMANN T/AU
L8            135 S E3-E9
                  E HOFFMANN TOR/AU
L9             57 S E4
                  E LENZ B/AU
L10            29 S E3-E9
                  E SLEIGHT A/AU
L11            52 S E4,E6-E8
                  E VANKAN P/AU
L12            23 S E3-E5
                  E ROCHE/PA,CS
L13         21472 S E3,E4
L14            61 S E27-E46
                  E ROHAN/PA,CS
L15             2 S E3,E4
L16            10 S L4 AND L5-L15
                  E PROSTATE/CT
                  E E5+ALL
L17          2309 S E2
L18          1988 S E12
```

```
L19       22609 S E20-E19+NT
L20           1 S L4 AND L17-L19
L21           1 S L4 AND (BPH OR BENIGN (L) PROSTAT? (L) (HYPERPLAS? OR HYPERTR
L22           1 S L20,L21
L23           1 S L22 AND L16
L24         969 S (NK OR NEUROKININ OR NEURO KININ)()1 (L) RECEPTOR (L) (ANTAGO
L25           5 S L24 AND L17-L19
L26           2 S L24 AND (BPH OR BENIGN (L) PROSTAT? (L) (HYPERPLAS? OR HYPERT
L27           6 S L25,L26
L28           1 S L23 AND L27
L29           5 S L27 NOT L28
                SEL DN AN 1 4 5
L30           3 S E1-E7 AND L29
L31           4 S L28,L30 AND (NK OR NK1 OR NEUROKININ OR TACHYKIN? OR RECEPTOR
L32           4 S L28,L30,L31
L33          39 S L4 AND (PD<=20010423 OR PRD<=20010423 OR AD<=20010423)
L34          47 S GR205171 OR GR()(205171 OR 205 171)
L35           5 S HSP117 OR HSP 117
L36          36 S L703606 OR L()(703606 OR 703 606)
L37          23 S L668169 OR L()(668169 OR 668 169)
L38           4 S LY303241 OR LY()(303241 OR 303 241)
L39          12 S LY306740 OR LY()(306740 OR 306 740)
L40          21 S MK869 OR MK 869
L41           6 S R544 OR R 544
L42           5 S SPANTIDE III
L43          11 S WIN62577 OR WIN()(62577 OR 62 577)
L44           5 S GR103537 OR GR()(103537 OR 103 537)
L45          13 S L758298 OR L()(758298 OR 758 298)
L46           9 S NKP608 OR NKP 608
L47          17 S CGP49823 OR CGP()(49823 OR 49 823)
L48         494 S CP96345 OR CP()(96345 OR 96 345)
L49         246 S CP99994 OR CP()(99994 OR 99 994)
L50          24 S CP122721 OR CP()(122721 OR 122 721)
L51         129 S FK888 OR FK 888
L52         119 S GR82334 OR GR()(82334 OR 82 334)
L53          41 S GR94800 OR GR()(94800 OR 94 800)
L54          20 S L733060 OR L()(733060 OR 733 060)
L55          16 S L742694 OR L()(742694 OR 742 694)
L56          10 S L754030 OR L()(754030 OR 754 030)
L57          30 S LY303870 OR LY()(303870 OR 303 870)
L58           9 S MEN11149 OR MEN()(11149 OR 11 149)
L59          10 S PD154075 OR PD()(154075 OR 154 075)
L60         250 S RP67580 OR RP()(67580 OR 67 580)
L61          18 S RPR100893 OR RPR()(100893 OR 100 893)
L62           1 S SPENDIDE
L63          32 S SENDIDE
L64          55 S SPANTIDE II
L65         217 S SR140333 OR SR()(140333 OR 140 333)
L66           0 S WIN41708 OR WIN()(41708 OR 41 708)
L67          11 S WIN62577 OR WIN()(62577 OR 62 577)
L68         410 S SR48968 OR SR()(48968 OR 48 968)
L69          69 S L659877 OR L()(659877 OR 659 877)
L70          74 S MEN10627 OR MEN()(10627 OR 10 627)
L71          14 S SR144190 OR SR()(144190 OR 144 190)
L72          41 S GR94800 OR GR()(94800 OR 94 800)
L73         149 S SR142801 OR SR()(142801 OR 142 801)
L74         159 S R820 OR R 820
L75          14 S R486 OR R 486
L76          13 S SB222200 OR SB()(222200 OR 222 200)
L77          13 S L758298 OR L()(758298 OR 758 298)
L78           0 S NK608 OR NK 608
L79           3 S MK608 OR MK 608
L80           2 S CGP47899 OR CGP()(47899 OR 47 899)
```

```
L81           16 S MEN11467 OR MEN()(11467 OR 11 467)
L82           18 S GR203040 OR GR()(203040 OR 203 040)
L83           13 S L732138 OR L()(732138 OR 732 138)
L84            1 S L4 AND L34-L83
L85            2 S WIN41908 OR WIN()(41908 OR 41 908)
L86          349 S SPANTIDE
L87            1 S L4 AND L85,L86
L88            1 S L84,L87
                 SEL RN

     FILE 'REGISTRY' ENTERED AT 07:50:53 ON 04 MAR 2003
L89          186 S E8-E193
L90          129 S L89 AND L3
L91            1 S 351383-26-1
L92           56 S L89 NOT L90,L91
L93            7 S 123-90-0 OR 3282-30-2 OR 4548-45-2 OR 16419-60-6 OR 139911-29
L94            6 S 471938-15-5 OR 474026-15-8 OR 474026-16-9 OR 474026-17-0 OR 4
L95           43 S L92 NOT L93,L94
L96            6 S 144177-32-2 OR 351383-26-1 OR 170729-80-3 OR 145194-26-9 OR 1

     FILE 'REGISTRY' ENTERED AT 07:57:44 ON 04 MAR 2003
L97           46 S L95,L96

     FILE 'HCAPLUS' ENTERED AT 07:58:26 ON 04 MAR 2003
L98          964 S L97
L99            3 S L4 AND L98
L100           3 S L88,L99
L101           3 S L100 AND L4-L16
L102           6 S L32,L101
                 E TACKYKININ RECEPTOR/CT
                 E TACHYKININ RECEPTOR/CT
L103        1581 S E5,E6
L104         223 S E14
                 E E4+ALL
L105        3707 S E10,E11,E9+NT
                 E E27+ALL
L106        2037 S E8,E7+NT
                 E E6+ALL
L107        3401 S E7,E8,E6+NT
                 E E20
L108        2087 S E3-E21
L109         638 S E22-E25
L110          13 S L4 AND L103-L109
L111           3 S L102 AND L110
L112           6 S L102,L111
L113           6 S L112 AND L4-L88
L114           3 S L113 AND L17-L19
L115           2 S L113 AND (BHP OR BENIGN(L)PROSTAT?(L)HYPER?)
L116           4 S L114,L115
L117          12 S L110,L113 NOT L116
L118          12 S L117 AND L4-L88,L98-L109

     FILE 'REGISTRY' ENTERED AT 08:04:28 ON 04 MAR 2003

     FILE 'HCAPLUS' ENTERED AT 08:04:40 ON 04 MAR 2003

     FILE 'EMBASE' ENTERED AT 08:05:33 ON 04 MAR 2003
                 E BENIGN PROSTAT/CT
                 E E4+ALL
                 E E2+ALL
L119        9419 S E1
L120        6565 S E7/BI OR E8/BI OR E11-E21/BI
L121        6986 S BHP OR BENIGN(L)PROSTAT?(L)HYPER?
```

```
L122          0 S L3
L123       1337 S L24
                E NERUOKININE 1 RECEPTOR ANTAGONIST/CT
                E NEUROKININE 1 RECEPTOR ANTAGONIST/CT
                E NEUROKININ 1 RECEPTOR ANTAGONIST/CT
                E E3+ALL
L124        663 S E1+NT
L125          1 S L119-L121 AND L123,L124

     FILE 'MEDLINE' ENTERED AT 08:08:33 ON 04 MAR 2003
L126          0 S L3
L127      13566 S L120 OR L121
                E BENIGN PROSTAT/CT
                E E5+ALL
                E E2+ALL
L128      11113 S E5+NT
L129       1074 S E17/BI OR E23/BI
L130      13795 S L127-L129
L131       1451 S L24
                E NEUROKININ 1 RECEPTOR/CT
                E E4+ALL
                E E2+ALL
L132       2169 S E15+NT
L133       2169 S E15/CN
L134       3283 S E14+NT
L135        680 S E14/CN
L136          0 S L130 AND L131-L135

     FILE 'EMBASE' ENTERED AT 08:10:58 ON 04 MAR 2003

     FILE 'WPIX' ENTERED AT 08:11:12 ON 04 MAR 2003
L137       2559 S L120/BIX OR L121/BIX OR L129/BIX
L138        168 S L24/BIX
L139        246 S (TACHYKININ(L)RECEPTOR)/BIX
L140         13 S L137 AND L138,L139
L141          6 S L140 AND F431/M0,M1,M2,M3,M4,M5,M6
L142      17637 S (B07-D04 OR B07-D04B OR B07-D04C OR C07-D04 OR C07-D04B OR C0
L143      13892 S (B06-H OR C06-H)/MC
L144          4 S L140 AND L142,L143
L145          6 S L141,L144
                SEL DN AN 1 6
L146          2 S E1-E4 AND L145

     FILE 'HCAPLUS' ENTERED AT 08:19:31 ON 04 MAR 2003
                SEL PN APPS L16

     FILE 'WPIX' ENTERED AT 08:19:54 ON 04 MAR 2003
L147         10 S E5-E97
L148          1 S L147 AND L137
L149          1 S L147 AND A61P013/IC,ICM,ICS,ICA,ICI
L150          0 S L148,L149 NOT L146
```